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NEWS 1	.	Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Jun 03	New e-mail delivery for search results now available
NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 11	Oct 24	BEILSTEIN adds new search fields
NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 13	Nov 18	DKILIT has been renamed APOLLIT
NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
NEWS 16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 20	EVENTLINE will be removed from STN
NEWS 28	Mar 24	PATDPAFULL now available on STN
NEWS 29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 30	Apr 11	Display formats in DGENE enhanced
NEWS 31	Apr 14	MEDLINE Reload
NEWS 32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 33	Apr 21	Indexing from 1947 to 1956 being added to records in CA/CAPLUS
NEWS 34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 35	Apr 28	RDISCLOSURE now available on STN
NEWS 36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 39	May 16	CHEMREACT will be removed from STN
NEWS 40	May 19	Simultaneous left and right truncation added to WSCA
NEWS 41	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation

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 NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
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 NEWS WWW      CAS World Wide Web Site (general information)

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FILE 'HOME' ENTERED AT 17:55:31 ON 27 MAY 2003

=> file medline, biosis, dgene, embase, wpids, uspatful
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.21       0.21

FILE 'MEDLINE' ENTERED AT 17:55:50 ON 27 MAY 2003

FILE 'BIOSIS' ENTERED AT 17:55:50 ON 27 MAY 2003
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=> s thrombin derived peptide or tp508
L1          59 THROMBIN DERIVED PEPTIDE OR TP508

=> s cartilage repair
L2        1879 CARTILAGE REPAIR

=> s chondrocyte
L3       24953 CHONDROCYTE

=> s l1 and l3
L4           3 L1 AND L3

=> d l4 ti abs ibib tot

L4   ANSWER 1 OF 3  BIOSIS  COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI   Thrombin and thrombin peptide TP508 (Chrysalin(R)) bind to a
     high affinity receptor that appears to be larger than known members of the
     proteolytically activated receptor (PAR) family.
ACCESSION NUMBER:    2002:165448  BIOSIS
DOCUMENT NUMBER:     PREV200200165448
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TITLE: Thrombin and thrombin peptide **TP508** (Chrysalin(R)) bind to a high affinity receptor that appears to be larger than known members of the proteolytically activated receptor (PAR) family.
AUTHOR(S): Bergmann, John S. (1); Laird, Aaron C.; Carney, Darrell H.
CORPORATE SOURCE: (1) Human Biological Chemistry and Genetics, University of Texas Medical Branch, 301 University Blvd., Galveston, TX, 77555 USA
SOURCE: Molecular Biology of the Cell, (Nov, 2001) Vol. 12, No. Supplement, pp. 330a. http://www.molbiolcell.org/. print. Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology Washington DC, USA December 08-12, 2001 ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 2 OF 3 USPATFULL
TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an NPAR agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:344424 USPATFULL
TITLE: Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S): Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002198154	A1	20021226
APPLICATION INFO.:	US 2002-50688	A1	20020116 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-909348, filed on 19 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
LINE COUNT: 862
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 3 OF 3 USPATFULL
TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating cartilage growth, repair or

regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an NPAR agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:78716 USPATFULL
TITLE:	Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S):	Carney, Darrell H., Dickinson, TX, UNITED STATES Crowther, Roger S., League City, TX, UNITED STATES Stiernberg, Janet, Paris, TX, UNITED STATES Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S):	The Board of Regents, The University of Texas System (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002042373	A1	20020411
APPLICATION INFO.:	US 2001-909348	A1	20010719 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS:	21
EXEMPLARY CLAIM:	1
LINE COUNT:	836

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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(FILE 'HOME' ENTERED AT 17:55:31 ON 27 MAY 2003)

FILE 'MEDLINE, BIOSIS, DGENE, EMBASE, WPIDS, USPATFULL' ENTERED AT 17:55:50 ON 27 MAY 2003

L1	59	S THROMBIN DERIVED PEPTIDE OR TP508
L2	1879	S CARTILAGE REPAIR
L3	24953	S CHONDROCYTE
L4	3	S L1 AND L3

=> d l3 ti abs ibib 1-5

L3 ANSWER 1 OF 24953 MEDLINE

TI Tissue-specific gene expression in chondrocytes grown on three-dimensional hyaluronic acid scaffolds.

AB The re-differentiation capacities of human articular and chick embryo sternal chondrocytes were evaluated by culture on HYAFF-11 and its sulphate derivative, HYAFF-11-S, polymers derived from the benzyl esterification of hyaluronate. Initial results showed that the HYAFF-11-S material promoted the highest rate of **chondrocyte** proliferation. RNA isolated from human and chick embryo chondrocytes cultured in Petri dishes, HYAFF-11 or HYAFF-11-S were subjected to semi-quantitative RT-PCR analyses. Human collagen types I, II, X, human Sox9 and aggrecan, chick collagen types I, II, IX and X were analysed. Results showed that human

collagen type II mRNA expression was upregulated on HYAFF-11 biomaterials. In particular, a high level of collagen type IIB expression was associated with three-dimensional culture conditions, and the HYAFF-11 material was the most supportive for human collagen type X mRNA expression. Human Sox9 mRNA levels were constantly maintained in monolayer cell culture conditions over a period of 21 days, while these were upregulated when chondrocytes were cultured on HYAFF-11 and HYAFF-11S. Furthermore, chick collagen type IIA and IIB mRNA expression was detected after only 7 days of HYAFF-11 culture. Chick collagen type IX mRNA expression decreased in scaffold cultures over time. Histochemical staining performed in engineered cartilage revealed the presence of a de novo synthesized glycosaminoglycan-rich extracellular matrix; immunohistochemistry confirmed the deposition of collagen type II. This study showed that the three-dimensional HYAFF-11 culture system is both an effective **chondrocyte** delivery system for the treatment of articular cartilage defects, and an excellent in vitro model for studying cartilage differentiation.

ACCESSION NUMBER: 2003240883 IN-PROCESS
DOCUMENT NUMBER: 22647955 PubMed ID: 12763454
TITLE: Tissue-specific gene expression in chondrocytes grown on three-dimensional hyaluronic acid scaffolds.
AUTHOR: Girotto Davide; Urbani Serena; Brun Paola; Renier Davide; Barbucci Rolando; Abatangelo Giovanni
CORPORATE SOURCE: Dipartimento di Istologia, Microbiologia e Biotecnologie Mediche, Facolta di Medicina, Universita di Padova, Viale G, 3 35121, Colombo, Italy.
SOURCE: BIOMATERIALS, (2003 Aug) 24 (19) 3265-75. Journal code: 8100316. ISSN: 0142-9612.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030524
Last Updated on STN: 20030524

L3 ANSWER 2 OF 24953 MEDLINE
TI Cross-linked type I and type II collagenous matrices for the repair of full-thickness articular cartilage defects-A study in rabbits.
AB The physico-chemical properties of collagenous matrices may determine the tissue response after insertion into full-thickness articular cartilage defects. In this study, cross-linked type I and type II collagen matrices, with and without attached chondroitin sulfate, were implanted into full-thickness defects in the femoral trochlea of adolescent rabbits. The tissue response was evaluated 4 and 12 weeks after implantation by general histology and two semi-quantitative histological grading systems.Four weeks after implantation, type I collagenous matrices were completely filled with cartilage-like tissue. By contrast, type II collagenous matrices revealed predominantly cartilaginous tissue only at the superficial zone and at the interface of the matrix with the subchondral bone, leaving large areas of the matrix devoid of tissue. Attachment of chondroitin sulfate appeared to promote cellular ingrowth and cartilaginous tissue formation in both types of collagen matrices.Twelve weeks after implantation, the differences between the matrices were less pronounced. The deep parts of the subchondral defects were largely replaced by new bone with a concomitant degradation of the matrices. The original cartilage contours in defects with type I collagen-based matrices were repaired with fibro-cartilaginous tissue. Defects containing type II matrices showed an increase in the amount of superficial cartilage-like tissue. The original contour, however, was not completely restored in all animals, occasionally leaving a central depression or fissure.It is concluded that different types of collagen matrices induce different tissue responses in full-thickness articular cartilage defects. Type I collagen-based matrices are superior to guide progenitor cells from a subchondral origin into the defect. In type II

collagen-based matrices cell migration is less, but invading cells are directed into a **chondrocyte** phenotype. Based on these observations it is suggested that a composite matrix consisting of a deep layer of type I collagen and a more superficial layer of type II collagen may be the matrix of choice for cartilage regeneration.

ACCESSION NUMBER: 2003240882 IN-PROCESS
DOCUMENT NUMBER: 22647954 PubMed ID: 12763453
TITLE: Cross-linked type I and type II collagenous matrices for the repair of full-thickness articular cartilage defects-A study in rabbits.
AUTHOR: Buma Pieter; Pieper Jeroen S; van Tienen Tony; van Susante Job L C; van der Kraan Peter M; Veerkamp Jacques H; van den Berg Wim B; Veth Rene P H; van Kuppevelt Toin H
CORPORATE SOURCE: Orthopedic Research Laboratory, Department of Orthopedics, University Medical Center Nijmegen, P.O. Box 9101, 6500 HB, Nijmegen, The Netherlands.
SOURCE: BIOMATERIALS, (2003 Aug) 24 (19) 3255-63. Journal code: 8100316. ISSN: 0142-9612.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030524
Last Updated on STN: 20030524

L3 ANSWER 3 OF 24953 MEDLINE
TI Establishing the protein MIA (melanoma inhibitory activity) as a marker for **chondrocyte** differentiation.
AB Melanoma inhibitory activity (MIA), also referred to as cartilage derived retinoic acid-sensitive protein (CD-RAP), is detected physiologically in cartilage tissue and pathologically in malignant melanomas. To measure MIA/CD-RAP quantitatively we developed a sensitive ELISA system. Recently, we described diagnostic applications of the MIA-ELISA in patients with cartilage diseases. The study described herein was performed to determine whether there is any relation between MIA/CD-RAP levels and the degree of **chondrocyte** differentiation in tissue culture and to analyse whether MIA/CD-RAP may serve as a useful marker to control **chondrocyte** differentiation in in vitro tissue engineering. Our data provide evidence that measuring MIA in tissue culture supernatant by a quantitative ELISA can be used as a marker for differentiated chondrocytes.

ACCESSION NUMBER: 2003240880 IN-PROCESS
DOCUMENT NUMBER: 22647951 PubMed ID: 12763450
TITLE: Establishing the protein MIA (melanoma inhibitory activity) as a marker for **chondrocyte** differentiation.
AUTHOR: Bosserhoff Anja K; Buettner Reinhard
CORPORATE SOURCE: Institutes of Pathology, University of Regensburg, Franz-Josef-Strauss-Allee 11, D-93053, Regensburg, Germany.
SOURCE: BIOMATERIALS, (2003 Aug) 24 (19) 3229-34. Journal code: 8100316. ISSN: 0142-9612.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030524
Last Updated on STN: 20030524

L3 ANSWER 4 OF 24953 MEDLINE
TI HIF-1alpha controls extracellular matrix synthesis by epiphyseal chondrocytes.
AB The transcription factor HIF-1alpha plays a crucial role in modifying gene expression during low oxygen tension. In a previous study, we demonstrated that HIF-1alpha is essential for **chondrocyte** growth arrest and survival in vivo. To explore further the role of HIF-1alpha in

cartilage biology, we undertook studies with primary epiphyseal chondrocytes with a targeted deletion of HIF-1alpha. In this study, we show that HIF-1alpha is necessary for regulating glycolysis under aerobic and anaerobic conditions. HIF-1alpha-null chondrocytes were unable to maintain ATP levels in hypoxic microenvironments, indicating a fundamental requirement for this factor for the regulation of **chondrocyte** metabolism. Synthesis of the angiogenic factor vascular endothelial growth factor was also significantly induced by hypoxia, and this increase is lost in HIF-1alpha-null mutant cells. Under hypoxic conditions, aggrecan mRNA and protein levels were significantly reduced in chondrocytes lacking the HIF-1alpha transcription factor. Interestingly, strongly increased type-II collagen protein levels were detected in wild-type cells after 44 hours of hypoxia. In addition, type-II collagen mRNA and protein levels were strongly decreased under low oxygen in chondrocytes lacking HIF-1alpha. In summary, our results clearly demonstrate the importance of HIF-1alpha in maintenance of anaerobic glycolysis, and thereby extracellular matrix synthesis, of epiphyseal chondrocytes.

ACCESSION NUMBER: 2003237665 IN-PROCESS
DOCUMENT NUMBER: 22552494 PubMed ID: 12665562
TITLE: HIF-1alpha controls extracellular matrix synthesis by epiphyseal chondrocytes.
AUTHOR: Pfander David; Cramer Thorsten; Schipani Ernestina; Johnson Randall S
CORPORATE SOURCE: Division of Orthopedic Rheumatology, Department of Orthopedic Surgery, University of Erlangen-Nuremberg, 91054 Erlangen, Germany.
CONTRACT NUMBER: CA 082515 (NCI)
SOURCE: JOURNAL OF CELL SCIENCE, (2003 May 1) 116 (Pt 9) 1819-26. Journal code: 0052457. ISSN: 0021-9533.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030523
Last Updated on STN: 20030523

L3 ANSWER 5 OF 24953 MEDLINE
TI Partial characterization of cell-type X collagen interactions.
AB Type X collagen is a short-chain non-fibrillar collagen that is deposited exclusively at sites of new bone formation. Although this collagen has been implicated in **chondrocyte** hypertrophy and endochondral ossification, its precise function remains unclear. One possible function could be to regulate the processes of **chondrocyte** hypertrophy through direct cell-type X collagen interactions. Adhesions of embryonic chick chondrocytes, and cell lines with known expression of collagen-binding integrins (MG63 and HOS), were assayed on chick type X collagen substrates, including the native, heat-denatured and pepsin-digested collagen, and the isolated C-terminal non-collagenous (NC1) domain. Type X collagen supported the greatest level of adhesion for all cell types tested. The involvement of the alpha2beta1 integrin in type X collagen-cell interaction was demonstrated by adhesion studies in the presence of Mg(2+) and Ca(2+) ions and integrin-function-blocking antibodies. Cells expressing alpha2beta1 integrin (chick chondrocytes and MG63 cells) also adhered to heat-denatured type X collagen and the isolated NC1 domain; however, removal of the non-collagenous domains by limited pepsinization of type X collagen resulted in very low levels of adhesion. Both focal contacts and actin stress-fibre formation were apparent in cells plated on type X collagen. The presence of alpha2 and beta1 integrin subunits in isolated chondrocytes and epiphyseal cartilage was also confirmed by immunolocalization. Our results demonstrate, for the first time, that type X collagen is capable of interacting directly with chondrocytes and other cells, primarily via alpha2beta1 integrin. These findings are atypical from the fibrillar collagen-cell interactions

via collagen binding integrins in that: (1) the triple-helical conformation is not strictly required for cell adhesion; (2) the NC1 domain is also involved in the adhesion of alpha2beta1-expressing cells. These data form the basis for further studies into the mechanism and biological significance of type X collagen deposition in the growth plate.

ACCESSION NUMBER: 2003235433 IN-PROCESS
DOCUMENT NUMBER: 22642469 PubMed ID: 12617725
TITLE: Partial characterization of cell-type X collagen interactions.
AUTHOR: Luckman Steven P; Rees Elaine; Kwan Alvin P L
CORPORATE SOURCE: Cardiff School of Biosciences, Cardiff University, PO Box 911, Museum Avenue, Cardiff, Wales, U.K.
SOURCE: BIOCHEMICAL JOURNAL, (2003 Jun 1) 372 (Pt 2) 485-93. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030522
Last Updated on STN: 20030522

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(FILE 'HOME' ENTERED AT 17:55:31 ON 27 MAY 2003)

FILE 'MEDLINE, BIOSIS, DGENE, EMBASE, WPIDS, USPATFULL' ENTERED AT 17:55:50 ON 27 MAY 2003

L1 59 S THROMBIN DERIVED PEPTIDE OR TP508
L2 1879 S CARTILAGE REPAIR
L3 24953 S CHONDROCYTE
L4 3 S L1 AND L3

=> s chondrocyte () bone
L5 15 CHONDROCYTE (W) BONE

=> d l5 ti abs ibib 1-5

L5 ANSWER 1 OF 15 MEDLINE
TI Bone formation following intrarenal transplantation of isolated murine chondrocytes: **chondrocyte-bone** cell transdifferentiation?.
AB Isolated syngeneic epiphyseal chondrocytes transplanted into a muscle formed cartilage in which matrix resorption and endochondral ossification began at the end of the second week after transplantation. After 56 days cartilage was converted into an ossicle. In 7-day-old intrarenal transplants, epiphyseal chondrocytes formed nodules of cartilage. In 10-day-old transplants, islands of bone appeared. Slight resorption of cartilage was first noted in 14-day-old transplants of chondrocytes. After eight weeks, transplants contained mainly bone. Intramuscularly transplanted rib chondrocytes formed cartilage which did not ossify. Nevertheless, bone islands appeared in intrarenal transplants of rib chondrocytes. Bone was not formed in allogeneic intrarenal transplants of epiphyseal or rib chondrocytes, but appeared in such transplants in animals immunosuppressed by anti-thymocyte serum and procarbazine. When spleen cells from animals immunized with allogeneic chondrocytes were transferred to immunosuppressed chondrocyte recipients two weeks after intrarenal chondrocyte transplantation, the majority of osteocytes in bone islands was dead. On the other hand, endochondral bone formed in intramuscular transplants of allogenic epiphyseal chondrocytes in immunosuppressed recipients was not damaged by sensitized spleen cells. This suggested that bone in 10- to 14-day-old intrarenal transplants of chondrocytes arose from injected cells and not by induction. To see whether bone was formed by chondrocytes or by some cells contaminating the

chondrocyte suspension, the superficial layer of rib cartilage was removed by collagenase digestion and only more central chondrocytes were used for transplantation. (ABSTRACT TRUNCATED AT 250 WORDS)

ACCESSION NUMBER: 90126382 MEDLINE
DOCUMENT NUMBER: 90126382 PubMed ID: 2612374
TITLE: Bone formation following intrarenal transplantation of isolated murine chondrocytes: **chondrocyte-bone** cell transdifferentiation?.
AUTHOR: Moskalewski S; Malejczyk J
CORPORATE SOURCE: Department of Histology and Embryology, Medical Academy, Warsaw, Poland.
SOURCE: DEVELOPMENT, (1989 Nov) 107 (3) 473-80. Journal code: 8701744. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199003
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19900308

L5 ANSWER 2 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Molecular imaging of the skeleton: Quantitative real-time bioluminescence monitoring gene expression in bone repair and development.
AB Monitoring gene expression in vivo, noninvasively, is a critical issue in effective gene therapy systems. To date, there are no adequate molecular imaging techniques, which quantitatively monitor gene expression in vivo in skeletal development and repair. The aim of this study was to monitor gene expression in skeletal development and repair, using a real-time molecular imaging system, which quantitatively and noninvasively detects bioluminescence in vivo. Our experimental model consisted of transgenic mice harboring the luciferase marker gene under the regulation of the human osteocalcin (hOC) promoter. A new light detection cooled charge coupled device (CCCD) camera was applied to monitor luciferase expression. In vitro, mesenchymal stem cells (MSCs) isolated from bone marrow of transgenic mice exhibited hOC promoter regulation, detected by luciferase expression that correlated with their osteogenic differentiation. During development from 1 week to 1.5 years, transgenic mice exhibited transgene expression in a wide spectrum of skeletal organs, including calvaria, vertebra, tail, and limbs, reaching a peak at 1 week in most of the skeletal organs. In two skeletal repair models, bone fracture and marrow ablation, the noninvasive CCCD system revealed a peak of luciferase expression at 6 days postsurgery. All quantitative, noninvasive, real-time CCCD measurements correlated with a luciferase biochemical assay and luciferase immunohistochemistry, which demonstrated luciferase expression in hypertrophic chondrocytes and trabecular osteoblasts. Our studies show for the first time (1) the CCCD detection system is a reliable quantitative gene detection tool for the skeleton in vivo, (2) expression of luciferase regulated by the hOC promoter is significantly decreased with age in most skeletal sites, and (3) the dynamics of hOC regulation during mice skeletal development and repair in real time, quantitatively and noninvasively.

ACCESSION NUMBER: 2003:163288 BIOSIS
DOCUMENT NUMBER: PREV200300163288
TITLE: Molecular imaging of the skeleton: Quantitative real-time bioluminescence monitoring gene expression in bone repair and development.
AUTHOR(S): Bar, Iris; Zilberman, Yoram; Zeira, Eveline; Galun, Eithan; Honigman, Alik; Turgeman, Gadi; Clemens, Thomas; Gazit, Zulma; Gazit, Dan (1)
CORPORATE SOURCE: (1) Skeletal Biotech Laboratory, Hebrew University, Hadassah Medical Center, Ein Kerem, PO Box 12272, Jerusalem, 91120, Israel: dgaz@cc.huji.ac.il Israel

SOURCE: Journal of Bone and Mineral Research, (March 2003, 2003) Vol. 18, No. 3, pp. 570-578. print. ISSN: 0884-0431.
DOCUMENT TYPE: Article
LANGUAGE: English

L5 ANSWER 3 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Regulation of BMP expression by thyroid hormone in differentiating chondrocytes.
ACCESSION NUMBER: 2001:573164 BIOSIS
DOCUMENT NUMBER: PREV200100573164
TITLE: Regulation of BMP expression by thyroid hormone in differentiating chondrocytes.
AUTHOR(S): Stewart, M. C. (1); Wang, Y. (1)
CORPORATE SOURCE: (1) Orthopaedics, Case Western Reserve University, Cleveland, OH USA
SOURCE: Journal of Bone and Mineral Research, (September, 2001) Vol. 16, No. Suppl. 1, pp. S320. print. Meeting Info.: Twenty-Third Annual Meeting of the American Society for Bone and Mineral Research Phoenix, Arizona, USA October 12-16, 2001 ISSN: 0884-0431.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L5 ANSWER 4 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI THE AMINO TERMINAL SEQUENCE OF THE DEVELOPMENTALLY REGULATED CH21 PROTEIN SHOWS HOMOLOGY WITH AMINO TERMINAL SEQUENCES OF LOW MOLECULAR WEIGHT PROTEINS BINDING HYDROPHOBIC MOLECULES.
AB Ch21 protein, a developmentally regulated chick embryo protein of 21,000 apparent molecular weight, was purified from culture medium of hypertrophic chondrocytes. The purification method included a DEAE cellulose chromatography column, a CM cellulose chromatography column and a HPLC molecular sieve column. The amino acid sequence of the amino terminal end of the protein was determined. Computer assisted analysis showed significant homology between this sequence and the amino terminal sequences of proteins that belong to the superfamily of the low molecular weight binding proteins sharing a basic framework for the binding and transport of small hydrophobic molecules. Determination of the amino terminal sequence of the chicken retinol binding protein excluded identity between this protein and the Ch21.
ACCESSION NUMBER: 1990:306076 BIOSIS
DOCUMENT NUMBER: BA90:25043
TITLE: THE AMINO TERMINAL SEQUENCE OF THE DEVELOPMENTALLY REGULATED CH21 PROTEIN SHOWS HOMOLOGY WITH AMINO TERMINAL SEQUENCES OF LOW MOLECULAR WEIGHT PROTEINS BINDING HYDROPHOBIC MOLECULES.
AUTHOR(S): CANCEDDA F D; ASARO D; MOLINA F; CANCEDDA R; CARUSO C; CAMARDELLA L; NEGRI A; RONCHI S
CORPORATE SOURCE: ISTITUTO NAZIONALE PER LA RICERCA SUL CANCRO, GENOA, ITALY.
SOURCE: BIOCHEM BIOPHYS RES COMMUN, (1990) 168 (3), 933-938. CODEN: BBRCA9. ISSN: 0006-291X.
FILE SEGMENT: BA; OLD
LANGUAGE: English

L5 ANSWER 5 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI BONE FORMATION FOLLOWING INTRARENAL TRANSPLANTATION OF ISOLATED MURINE CHONDROCYTES **CHONDROCYTE-BONE** CELL TRANSDIFFERENTIATION.
AB Isolated syngeneic chondrocytes transplanted into a muscle formed cartilage in which matrix resorption and endochondral ossification began at the end of the second week after transplantation. After 56 days cartilage was converted into an ossicle. In 7-day-old intrarenal

transplants, epiphyseal chondrocytes formed nodules of cartilage. In 10-day-old transplants, islands of bone appeared. Slight resorption of cartilage was first noted in 14-day-old transplants of chondrocytes. After eight weeks, transplants contained mainly bone. Intramuscularly transplanted rib chondrocytes formed cartilage which did not ossify. Nevertheless, bone islands appeared in intrarenal transplants of rib chondrocytes. Bone was not formed in allogeneic intrarenal transplants of epiphyseal or rib chondrocytes, but appeared in such transplants in animals immunosuppressed by anti-thymocyte serum and procarbazine. When spleen cells from animals immunized with allogeneic chondrocytes were transferred to immunosuppressed chondrocyte recipients two weeks after intrarenal chondrocyte transplantation, the majority of osteocytes in bone islands was dead. On the other hand, endochondral bone formed in intramuscular transplants of allogenic epiphyseal chondrocytes in immunosuppressed recipients was not damaged by sensitized spleen cells. This suggested that bone in 10- to 14-day-old intrarenal transplants of chondrocytes arose from injected cells and not by induction. To see whether bone was formed by chondrocytes or by some cells contaminating the chondrocyte suspension, the superficial layer of rib cartilage was removed by collagenase digestion and only more central chondrocytes were used for transplantation. Intrarenal transplants of these chondrocytes also yielded bone. Furthermore, in some experiments intrarenal transplants of syngeneic rib chondrocytes were stained in toto by Alcian blue and Alizarin red S 7 and 14 days after transplantation and examined under a dissecting microscope. In 7-day-old transplants only cartilage nodules could be found while in the older ones cartilage and bone or only bone islands were present. These results strongly suggest that in intrarenal transplants epiphyseal and rib chondrocytes transdifferentiated into bone cells. It also seems that chondrocytes transdifferentiated into bone cells. It also seems that chondrocytes first formed cartilage matrix which, after their transdifferentiation, was substituted by bone matrix.

ACCESSION NUMBER: 1990:152242 BIOSIS
DOCUMENT NUMBER: BA89:79660
TITLE: BONE FORMATION FOLLOWING INTRARENAL TRANSPLANTATION OF ISOLATED MURINE CHONDROCYTES **CHONDROCYTE-BONE** CELL TRANSDIFFERENTIATION.
AUTHOR(S): MOSKALEWSKI S; MALEJCZYK J
CORPORATE SOURCE: DEP. HISTOL. AND EMBRYOL., MED. ACAD., CHALUBINSKIEGO 5, PL-02-004 WARSAW, POLAND.
SOURCE: DEVELOPMENT (CAMB), (1989) 107 (3), 473-480. CODEN: DEVPED. ISSN: 0950-1991.
FILE SEGMENT: BA; OLD
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 17:55:31 ON 27 MAY 2003)

FILE 'MEDLINE, BIOSIS, DGENE, EMBASE, WPIDS, USPATFULL' ENTERED AT 17:55:50 ON 27 MAY 2003

L1 59 S THROMBIN DERIVED PEPTIDE OR TP508
L2 1879 S CARTILAGE REPAIR
L3 24953 S CHONDROCYTE
L4 3 S L1 AND L3
L5 15 S CHONDROCYTE () BONE

=> s l1 and l2
L6 2 L1 AND L2

=> d l6 ti abs ibib tot

L6 ANSWER 1 OF 2 USPATFULL
TI Stimulation of cartilage growth with agonists of the non-proteolytically

activated thrombin receptor

AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an NPAR agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:344424 USPATFULL

TITLE: Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor

INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES

PATENT ASSIGNEE(S): Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002198154	A1	20021226
APPLICATION INFO.:	US 2002-50688	A1	20020116 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-909348, filed on 19 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133

NUMBER OF CLAIMS: 28

EXEMPLARY CLAIM: 1

LINE COUNT: 862

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 2 OF 2 USPATFULL

TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor

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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:78716 USPATFULL

TITLE: Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor

INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES

PATENT ASSIGNEE(S): The Board of Regents, The University of Texas System (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002042373	A1	20020411
APPLICATION INFO.:	US 2001-909348	A1	20010719 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 836
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d his

(FILE 'HOME' ENTERED AT 17:55:31 ON 27 MAY 2003)

FILE 'MEDLINE, BIOSIS, DGENE, EMBASE, WPIDS, USPATFULL' ENTERED AT 17:55:50 ON 27 MAY 2003

L1 59 S THROMBIN DERIVED PEPTIDE OR TP508
L2 1879 S CARTILAGE REPAIR
L3 24953 S CHONDROCYTE
L4 3 S L1 AND L3
L5 15 S CHONDROCYTE () BONE
L6 2 S L1 AND L2

=> s l1 and cartilage formation
L7 2 L1 AND CARTILAGE FORMATION

=> s l7 non l6
MISSING OPERATOR L7 NON
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> d l7 ti abs ibib tot

L7 ANSWER 1 OF 2 USPATFULL
TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

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CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:344424 USPATFULL
TITLE: Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES

Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S): Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002198154	A1	20021226
APPLICATION INFO.:	US 2002-50688	A1	20020116 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-909348, filed on 19 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
LINE COUNT: 862
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 2 OF 2 USPATFULL
TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an NPAR agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:78716 USPATFULL
TITLE: Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S): The Board of Regents, The University of Texas System (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002042373	A1	20020411
APPLICATION INFO.:	US 2001-909348	A1	20010719 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 836

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> s thrombin derived peptide () cartilage
L8 0 THROMBIN DERIVED PEPTIDE (W) CARTILAGE

=> d his

(FILE 'HOME' ENTERED AT 17:55:31 ON 27 MAY 2003)

FILE 'MEDLINE, BIOSIS, DGENE, EMBASE, WPIDS, USPATFULL' ENTERED AT 17:55:50 ON 27 MAY 2003

L1 59 S THROMBIN DERIVED PEPTIDE OR TP508
L2 1879 S CARTILAGE REPAIR
L3 24953 S CHONDROCYTE
L4 3 S L1 AND L3
L5 15 S CHONDROCYTE () BONE
L6 2 S L1 AND L2
L7 2 S L1 AND CARTILAGE FORMATION
L8 0 S THROMBIN DERIVED PEPTIDE () CARTILAGE

=> s thrombin derived peptide () chondrocyte
L9 0 THROMBIN DERIVED PEPTIDE (W) CHONDROCYTE

=> d l1 ti abs ibib 1-10

L1 ANSWER 1 OF 59 MEDLINE

TI PAR1-dependent and independent increases in COX-2 and PGE2 in human colonic myofibroblasts stimulated by thrombin.

AB Subepithelial myofibroblast-derived prostaglandin E(2) (PGE(2)) regulates epithelial chloride secretion in the intestine. Thrombin is elevated in inflammatory conditions of the bowel. Therefore, we sought to determine a role for thrombin in regulating PGE(2) synthesis by colonic myofibroblasts. Incubation of cultured CCD-18Co colonic myofibroblasts with thrombin, the proteinase-activated receptor 1 (PAR(1))-activating peptide (Cit-NH(2)), and peptides corresponding to 2 noncatalytic regions of thrombin (TP367 and **TP508**) for 18 h increased both cyclooxygenase (COX)-2 expression (immunocytochemistry) and PGE(2) synthesis (enzyme immunoassay). Inhibition of thrombin by D-Phe-Pro-Arg-chloromethylketone (PPACK) did not significantly reduce PGE(2) synthesis, which remained elevated compared with control. We also investigated the basic fibroblast growth factor (bFGF) dependence of thrombin-induced PGE(2) elevations. Recombinant human bFGF concentration dependently increased PGE(2) synthesis, and a bFGF neutralizing antibody inhibited PGE(2) synthesis induced by TP367 and **TP508** (approximately 40%) and by thrombin (approximately 20%) (but not Cit-NH(2)). Thrombin, therefore, upregulates COX-2-derived PGE(2) synthesis by both catalytic cleavage of PAR(1) and bFGF-dependent noncatalytic activity. This presents a novel mechanism by which intestinal myofibroblasts might regulate epithelial chloride secretion.

ACCESSION NUMBER: 2003159038 MEDLINE
DOCUMENT NUMBER: 22562466 PubMed ID: 12505789
TITLE: PAR1-dependent and independent increases in COX-2 and PGE2 in human colonic myofibroblasts stimulated by thrombin.
AUTHOR: Seymour Michelle L; Zaidi Nosheen F; Hollenberg Morley D; MacNaughton Wallace K
CORPORATE SOURCE: Mucosal Inflammation Research Group, University of Calgary, Calgary, Alberta, Canada T2N 4N1.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY. CELL PHYSIOLOGY, (2003 May) 284 (5) C1185-92.
Journal code: 100901225. ISSN: 0363-6143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030406
Last Updated on STN: 20030522
Entered Medline: 20030521

L1 ANSWER 2 OF 59 MEDLINE
TI Controlled release of an osteogenic peptide from injectable biodegradable polymeric composites.
AB Poly(D,L-lactic-co-glycolic acid)/poly(ethylene glycol) (PLGA/PEG) blend microparticles loaded with the osteogenic peptide **TP508** were added to a mixture of poly(propylene fumarate) (PPF), poly(propylene fumarate)-diacrylate (PPF-DA), and sodium chloride (NaCl) for the fabrication of PPF composite scaffolds that could allow for tissue ingrowth as well as for the controlled release of **TP508** when implanted in an orthopedic defect site. In this study, PPF composites were fabricated and the in vitro release kinetics of **TP508** were determined. **TP508** loading within the PLGA/PEG microparticles, PEG content within the PLGA/PEG microparticles, the microparticle content of the PPF composite polymer component, and the leachable porogen initial mass percent of the PPF composites were varied according to a fractional factorial design and the effect of each variable on the release kinetics was determined for up to 28 days. Each composite formulation released **TP508** with a unique release profile. The initial release (release through day 1) of the PLGA/PEG microparticles was reduced upon inclusion in the PPF composite formulations. Day 1 normalized cumulative mass release from PPF composites ranged from 0.14+/-0.01 to 0.41+/-0.01, whereas the release from PLGA/PEG microparticles ranged from 0.31+/-0.02 to 0.58+/-0.01. After 28 days, PPF composites released 53+/-4% to 86+/-2% of the entrapped peptide resulting in cumulative mass releases ranging from 0.14+/-0.01 microg **TP508**/mm(3) scaffold to 2.46+/-0.05 microg **TP508**/mm(3) scaffold. The results presented here demonstrate that PPF composites can be used for the controlled release of **TP508** and that alterations in the composite's composition can lead to modulation of the **TP508** release kinetics. These composites can be used to explore the effects varied release kinetics and dosages on the formation of bone in vivo.

ACCESSION NUMBER: 2003004378 IN-PROCESS
DOCUMENT NUMBER: 22356120 PubMed ID: 12468217
TITLE: Controlled release of an osteogenic peptide from injectable biodegradable polymeric composites.
AUTHOR: Hedberg Elizabeth L; Tang Andrew; Crowther Roger S; Carney Darrell H; Mikos Antonios G
CORPORATE SOURCE: Department of Bioengineering, Rice University, PO Box 1892, MS-142, Houston, TX 77251-1892, USA.
CONTRACT NUMBER: R01-AR44381 (NIAMS)
R01-DE13031 (NIDCR)
T32-GM08362 (NIGMS)
SOURCE: JOURNAL OF CONTROLLED RELEASE, (2002 Dec 5) 84 (3) 137-50.
Journal code: 8607908. ISSN: 0168-3659.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030105
Last Updated on STN: 20030105

L1 ANSWER 3 OF 59 MEDLINE
TI Effects of thrombin peptides on wound healing and proliferation and migration of normal human epidermal keratinocyte (NHEK).
AB OBJECTIVE: To define the effects of thrombin peptides on wound healing and NHEK proliferation and migration. METHODS: A wound model was made with four 1.5 cm circular full thickness dermal excisions on the back of each

Sprague-Dawley rat. 0.1 microgram (40 microliter) **TP508** was applied to each circular excisional wound in 9 rats, the other 9 received saline only. Wound area was calculated with JAVA Jandel and IMAGE PRO software. NHEK945 proliferation was assessed by MTT assay and direct cell count with a Coulter Counter. Cell migration was determined by 48-well Boyden Chamber. Cells migrated onto the lower surface of the filter were assessed by a Chemi Imager 4000 Image Analyzer and expressed as spot density. RESULTS: Wound area in rats treated with **TP508** was 73.7% and 45.4% of saline control on day 7 and 14, respectively. NHEK945 proliferation was accelerated after adding thrombin and **TP508**. The spot density of migrated cells was 76.7 plus minus 13.8 in medium alone. After adding 1 microgram/ml of thrombin and 10 microgram/ml of **TP508**, the spot density was 104.4 plus minus 12.2 and 109.4 plus minus 14.6, respectively. CONCLUSION: Results of this study suggest that both thrombin and **TP508** have significant actions on wound healing and NHEK proliferation and migration, which is important in wound repair.

ACCESSION NUMBER: 2002344571 MEDLINE
DOCUMENT NUMBER: 21866780 PubMed ID: 11876838
TITLE: Effects of thrombin peptides on wound healing and proliferation and migration of normal human epidermal keratinocyte (NHEK).
AUTHOR: Huang Y; Yang Z; Carney D
CORPORATE SOURCE: Institute of Burn Research, Southwestern Hospital, Third Military Medical University, Chongqing 400038.
SOURCE: Zhonghua Shao Shang Za Zhi, (2000 Feb) 16 (1) 26-9. Journal code: 100959418. ISSN: 1009-2587.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020629
Last Updated on STN: 20020713
Entered Medline: 20020712

L1 ANSWER 4 OF 59 MEDLINE
TI Thrombin peptide, **TP508**, stimulates angiogenic responses in animal models of dermal wound healing, in chick chorioallantoic membranes, and in cultured human aortic and microvascular endothelial cells.
AB The alpha-thrombin peptide, **TP508**, accelerates the healing of full-thickness wounds in both normal and ischemic skin. In wounds treated with **TP508**, a pattern of increased vascularization is consistently observed both grossly and microscopically when compared to wounds treated with saline. One possible mechanism by which the peptide accelerates wound healing is by promoting revascularization of granulation tissue at the injured site. To evaluate the angiogenic potential of **TP508**, the peptide was tested in the chick embryo chorioallantoic membrane (CAM), where it increased the density and size of CAM blood vessels relative to controls. Additionally, **TP508** stimulated chemokinesis and chemotaxis in a dose-dependent fashion in cultured human aortic and human microvascular endothelial cells. Taken together, these in vivo and in vitro data support an angiogenic role for **TP508** in wound healing. A working model is presented to explain how this 23-amino-acid peptide, which lacks proteolytic activity, is generated during wound healing and contributes to the nonproteolytic functions associated with alpha-thrombin during tissue repair.

ACCESSION NUMBER: 2002157334 MEDLINE
DOCUMENT NUMBER: 21886336 PubMed ID: 11888680
TITLE: Thrombin peptide, **TP508**, stimulates angiogenic responses in animal models of dermal wound healing, in chick chorioallantoic membranes, and in cultured human aortic and microvascular endothelial cells.
AUTHOR: Norfleet A M; Bergmann J S; Carney D H

CORPORATE SOURCE: Chrysalis BioTechnology, Inc., 2200 Market Street, Suite 600, Galveston, TX 77550, USA.
SOURCE: GENERAL PHARMACOLOGY, (2000 Nov) 35 (5) 249-54. Ref: 26
Journal code: 7602417. ISSN: 0306-3623.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020313
Last Updated on STN: 20020620
Entered Medline: 20020619

L1 ANSWER 5 OF 59 MEDLINE
TI An experimental study of the effects of thrombin receptor activating peptide (**TP508**) on healing of ischemic wound and flap survival in rats.
AB OBJECTIVE: To investigate the effects of the thrombin receptor activating peptide (**TP508**) on healing of ischemic wound and flap survival in rats. METHODS: Sixty-six Sprague-Dawley rats were employed as the model. On the back of the rats, three kinds of wound and flap were made to establish four groups as follows: partial ischemic wound in 16, full ischemic wound in 16, routine wound in 18 and flap in 16 rats. Each group was further divided into **TP508** treating group and isotonic saline control group. The total and necrotic areas of the wounds and flaps were daplicated on acetate papers and calculated with a computer on the 3rd, 7th, 10th and 14th post-operation days (PODs). RESULTS: In routine wounds, the ischemic wound area treated by **TP508** was 73.7% and 45.4% in saline control groups on 7 and 14 (PODs), respectively. While in the flap model, the necrotic flap area treated by **TP508** was 80.4% and 56.8% in control groups on 7 and 14 (PODs), respectively. CONCLUSION: **TP508** could accelerate healing of ischemic wound and improve flap survival in rats.
ACCESSION NUMBER: 2002125188 MEDLINE
DOCUMENT NUMBER: 21849128 PubMed ID: 11859609
TITLE: An experimental study of the effects of thrombin receptor activating peptide (**TP508**) on healing of ischemic wound and flap survival in rats.
AUTHOR: Huang Y; Yang Z; Li A
CORPORATE SOURCE: Institute of Burn Research, Southwestern Hospital, Third Military Medical University, Chongqing 400038, P. R. China.
SOURCE: Zhonghua Shao Shang Za Zhi, (2001 Dec) 17 (6) 339-41.
Journal code: 100959418. ISSN: 1009-2587.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020226
Last Updated on STN: 20020508
Entered Medline: 20020507

L1 ANSWER 6 OF 59 MEDLINE
TI Thrombin peptide **TP508** accelerates closure of dermal excisions in animal tissue with surgically induced ischemia.
AB **TP508** is a synthetic peptide corresponding to amino acids 508 through 530 of human prothrombin. We previously demonstrated that a single topical application of **TP508** stimulates revascularization and healing of acute incisional and excisional wounds in normal, healthy rat skin. To determine if **TP508** would enhance wound healing in ischemic skin, we used bipedicle flaps, cranially based flaps, and free grafts to surgically create ischemic regions on the backs of rats.

Full-thickness, circular excisions were made within the flaps or grafts and immediately treated with a single application of saline +/- **TP508** (0.1 microg/wound). Compared to wound closure in normal skin, ischemic skin wounds exhibited delayed closure, and the length of delay correlated with the degree of surgically induced ischemia. **TP508** significantly accelerated closure in both normal and ischemic skin, resulting in closure rates that were increased within the first 7 days of wounding by 30% in normal tissue and bipedicle flaps, 50% in cranially based flaps, and 225% in free grafts. Moreover, in both flap models, **TP508** restored the rate of closure to a rate approximating the control rate observed in normal skin. Histological comparisons of wound tissue from normal skin and cranially based flaps showed that ischemia reduced early recruitment of inflammatory cells at day 1 but increased inflammatory cell numbers in wound beds at day 14. **TP508** treatment of ischemic flap wounds significantly increased early inflammatory cell recruitment and restored the normal rapid resolution of the inflammatory phase. In addition, at day 7, **TP508**-treated wounds appeared to have an increased number of large functional blood vessels compared to saline controls. These studies support the potential efficacy of **TP508** in treating ischemic wounds in humans.

ACCESSION NUMBER: 2001285509 MEDLINE
DOCUMENT NUMBER: 21221250 PubMed ID: 11208179
TITLE: Thrombin peptide **TP508** accelerates closure of dermal excisions in animal tissue with surgically induced ischemia.
AUTHOR: Norfleet A M; Huang Y; Sower L E; Redin W R; Fritz R R; Carney D H
CORPORATE SOURCE: Department of Human Biological Chemistry and Genetics, The University of Texas Medical Branch, 301 University Blvd., Galveston, TX 77555-0645, USA.
CONTRACT NUMBER: R44 DK53580 (NIDDK)
SOURCE: WOUND REPAIR AND REGENERATION, (2000 Nov-Dec) 8 (6) 517-29. Journal code: 9310939. ISSN: 1067-1927.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010702
Last Updated on STN: 20010702
Entered Medline: 20010628

L1 ANSWER 7 OF 59 MEDLINE

TI Acceleration of full-thickness wound healing in normal rats by the synthetic thrombin peptide, **TP508**.

AB Thrombin is an essential factor in hemostasis, inflammation, and tissue repair. The synthetic thrombin peptide, **TP508**, binds to high-affinity thrombin receptors and mimics cellular effects of thrombin at sites of tissue injury. Treatment of full-thickness excisional wounds in normal rats with a single topical application of 0.1 microg **TP508** (14 pmol/cm2) reproducibly accelerates wound closure, yielding wounds that on average close 39% more than controls by day 7 ($p < 0.001$). Wounds treated with 1.0 microg **TP508** are 35% and 43% ($p < 0.001$) smaller than controls on day 7 and 10, respectively. The early rate of closure is approximately 40% greater in **TP508**-treated than vehicle-treated wounds (20 versus 14 mm2/day) and remains higher through day 7. Breaking strength after closure is slightly greater (15-23%) in wounds treated with **TP508** than with saline alone. Histologic comparisons show that **TP508** enhances recruitment of inflammatory cells to the wound site within 24 hours post-injury. **TP508** treatment also augments revascularization of injured tissue, as evidenced at day 7 by the larger size of functional vessels in the granulation tissue and by the directed development of blood vessels to

wounds. These studies raise the possibility that **TP508** may be clinically useful in management of open wounds.

ACCESSION NUMBER: 2000402971 MEDLINE
DOCUMENT NUMBER: 20345355 PubMed ID: 10886811
TITLE: Acceleration of full-thickness wound healing in normal rats by the synthetic thrombin peptide, **TP508**.
AUTHOR: Stiernberg J; Norfleet A M; Redin W R; Warner W S; Fritz R R; Carney D H
CORPORATE SOURCE: Department of Human Biological Chemistry and Genetics,The University of Texas Medical Branch, Galveston, Texas 77555-0645, USA.
CONTRACT NUMBER: DK-25807 (NIDDK)
GM-475472 (NIGMS)
SOURCE: WOUND REPAIR AND REGENERATION, (2000 May-Jun) 8 (3) 204-15. Journal code: 9310939. ISSN: 1067-1927.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000901
Last Updated on STN: 20000901
Entered Medline: 20000821

L1 ANSWER 8 OF 59 MEDLINE
TI Thrombin peptide, **TP508**, induces differential gene expression in fibroblasts through a nonproteolytic activation pathway.
AB Prior studies have shown that synthetic peptides representing the domain of thrombin responsible for high-affinity binding to fibroblasts stimulate chemotactic and cell proliferative signals through a nonproteolytic mechanism. One of these peptides, **TP508**, has recently been shown to be chemotactic for neutrophils, to enhance collagen accumulation in wounds, to enhance revascularization of wounds, and to accelerate the healing of incisional and open wounds in normal animals and in animals with impaired healing. To determine whether **TP508** activates the proteolytically activated receptor for thrombin (PAR1), or the signals that are activated by PAR1, we treated human fibroblasts with **TP508** and the PAR1-activating peptide, SFLLRNP, and analyzed the effects of these peptides on gene expression using differential display reverse transcriptase polymerase chain reaction. **TP508** induces expression of a number of specific message fragments with short tyrosine kinase-like domains that are not induced by SFLLRNP. Sequencing full-length clones prepared by Marathon extension of **TP508** -induced fragments revealed that among the induced transcripts, there was a sequence with 88% homology to human annexin V. Northern analysis with authentic annexin V cDNA confirms that **TP508**, but not SFLLRNP, induces expression of annexin V in human fibroblasts. These results demonstrate that **TP508** activates a cellular response separate from that activated through PAR1 and supports the hypothesis that **TP508** acts through a separate nonproteolytically activated thrombin receptor that may be responsible for high-affinity thrombin binding and for nonproteolytic signals that are required for thrombin stimulation of cell proliferation.

ACCESSION NUMBER: 1999167419 MEDLINE
DOCUMENT NUMBER: 99167419 PubMed ID: 10066370
TITLE: Thrombin peptide, **TP508**, induces differential gene expression in fibroblasts through a nonproteolytic activation pathway.
AUTHOR: Sower L E; Payne D A; Meyers R; Carney D H
CORPORATE SOURCE: The Department of Human Biological Chemistry and Genetics, The University of Texas Medical Branch, Galveston, Texas, 77555-0645, USA.
CONTRACT NUMBER: 5RO1 GM47572 (NIGMS)

SOURCE: EXPERIMENTAL CELL RESEARCH, (1999 Mar 15) 247 (2) 422-31.
Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990413

L1 ANSWER 9 OF 59 MEDLINE
TI Renal entactin (nidogen): isolation, characterization and tissue distribution.
AB Entactin/nidogen (E/N) was isolated from bovine renal tubular basement membrane. Apparent molecular weight, amino acid composition, and molecular configuration by electron microscopy rotary shadowing were similar to that of nidogen from EHS mouse tumor. The identity of bovine E/N was confirmed using a **thrombin derived peptide**, the sequence of which corresponded to a region within mouse and human E/N. Monoclonal and polyclonal anti-E/N antibodies were used to determine the distribution of E/N in human kidney by immunofluorescent and immunoelectron microscopy. E/N was present in all renal basement membranes and was distributed through the full width of the glomerular basement membrane (GBM) with accentuation along its epithelial aspects. E/N distribution was similar to that of novel collagen chain alpha 3(IV) NC domain in the GBM. In the mesangium, E/N was distributed mainly in the peripheral mesangial region that is bounded by the GBM, while classical collagen chain alpha 1(IV) NC as present diffusely throughout the mesangium. In the developing nephron, E/N was present in basement membranes of the ureteric bud, primitive vesicle and S-form. In all instances, E/N co-localized with laminin B2 chain. Prominent E/N detection within the mesangium was observed in diseases where mesangial expansion was present. This process was also seen in early diabetic nephropathy, but disappeared with disease progression. However, all thickened diabetic renal basement membranes showed an increase in E/N which was also present in Kimmelstiel-Wilson lesions. E/N was observed in the GBM "spikes" of membranous glomerulonephritis and in epithelial crescents associated with various disorders. The association between E/N, laminin and type IV collagen chains observed in the normal kidney were maintained in disorders with altered E/N distribution. We could not detect any changes in the distribution of E/N in other acquired and hereditary kidney diseases. These observations reflect the involvement of E/N in the structure and disease alteration of renal basement membranes and mesangial matrix.
ACCESSION NUMBER: 92079440 MEDLINE
DOCUMENT NUMBER: 92079440 PubMed ID: 1745013
TITLE: Renal entactin (nidogen): isolation, characterization and tissue distribution.
AUTHOR: Katz A; Fish A J; Kleppel M M; Hagen S G; Michael A F; Butkowski R J
CORPORATE SOURCE: Department of Pediatrics, University of Minnesota, Minneapolis.
CONTRACT NUMBER: AI10704 (NIAID)
DKO 07087 (NIDDK)
DKO 8232-01 (NIDDK)
+
SOURCE: KIDNEY INTERNATIONAL, (1991 Oct) 40 (4) 643-52.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199201

ENTRY DATE: Entered STN: 19920202
Last Updated on STN: 19960129
Entered Medline: 19920115

L1 ANSWER 10 OF 59 MEDLINE
TI Hormone-like activity of human thrombin.
AB Recently, we have shown that thrombin is a chemotaxin and growth-promoting agent for cells of the mononuclear phagocytic lineage. These activities are independent of thrombin's enzymatic activity. Unlike other chemotactic factors, thrombin is specific for monocytes and does not attract granulocytes. To further explore the cellular specificity we have used a human leukemia cell line HL-60 that is capable of in vitro differentiation toward either monocytes (HL-60/mono) following incubation with 1,25(OH)2D3, or granulocytes (HL-60/gran) following incubation with DMSO. In contrast to undifferentiated HL-60 cells or HL-60/gran, we find that HL-60/mono respond chemotactically to intact human alpha-thrombin, esterolytically inactive iPR2P-alpha-thrombin, and the **thrombin-derived peptide** CB67-129, previously shown to contain the thrombin chemotactic exosite. In addition, thrombin induces in HL-60/mono association of actin with the cytoskeleton and causes an increase in levels of free cytosolic Ca2+. These phenomena are well characterized as early events occurring concomitant with directed cell movement associated with exposure to chemotactic agents such as FMLP. Furthermore, in contrast to fibroblasts, both iPR2P-alpha-thrombin and the thrombin chemotactic peptide CB67-129 evoke dose-dependent [3H]TdR incorporation, protein synthesis, and cell replication in growth-arrested J-744 cells, a murine macrophage-like cell line. Limited tryptic digests of CB67-129 lose chemotactic activity but retain full mitogenic activity, demonstrating that as with PDGF, the sites on CB67-129 required for chemotaxis and mitogenesis are clearly dissociable. The mitogenic effects of the CB67-129 digest can be mimicked by a synthetic tetradecapeptide analogue of CB67-129 (residues 367-380) that includes the loop B insertion sequence, previously shown to be critical for thrombin's chemotactic effects. From these data, it is apparent that the loop B insertion is critical for thrombin's nonenzymic biological effects on cells, but additional sites are required for stimulation of cell movement.
ACCESSION NUMBER: 87182864 MEDLINE
DOCUMENT NUMBER: 87182864 PubMed ID: 3032049
TITLE: Hormone-like activity of human thrombin.
AUTHOR: Bar-Shavit R; Hruska K A; Kahn A J; Wilner G D
CONTRACT NUMBER: HL-14147 (NHLBI)
HL-34282 (NHLBI)
HL-34575 (NHLBI)
+
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1986) 485 335-48.
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198704
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19970203
Entered Medline: 19870429

=> d his

(FILE 'HOME' ENTERED AT 17:55:31 ON 27 MAY 2003)

FILE 'MEDLINE, BIOSIS, DGENE, EMBASE, WPIDS, USPATFULL' ENTERED AT 17:55:50 ON 27 MAY 2003
L1 59 S THROMBIN DERIVED PEPTIDE OR TP508

L2 1879 S CARTILAGE REPAIR
L3 24953 S CHONDROCYTE
L4 3 S L1 AND L3
L5 15 S CHONDROCYTE () BONE
L6 2 S L1 AND L2
L7 2 S L1 AND CARTILAGE FORMATION
L8 0 S THROMBIN DERIVED PEPTIDE () CARTILAGE
L9 0 S THROMBIN DERIVED PEPTIDE () CHONDROCYTE

=> d l1 ti abs ibib 40-50

L1 ANSWER 40 OF 59 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI PAR(1)-dependent and independent increases in COX-2 and PGE(2) in human colonic myofibroblasts stimulated by thrombin.
AB Sub epithelial myofibroblast-derived prostaglandin E(2) (PGE(2)) regulates epithelial chloride secretion in the intestine. Thrombin is elevated in inflammatory conditions of the bowel. Therefore, we sought to determine a role for thrombin in regulating PGE(2) synthesis by colonic myofibroblasts. Incubation of cultured CCD-18Co colonic myofibroblasts with thrombin, the proteinase-activated receptor 1 (PAR(1))-activating peptide (Cit-NH(2)), and peptides corresponding to 2 noncatalytic regions of thrombin (TP367 and **TP508**) for 18 h increased both cyclooxygenase (COX)-2 expression (immunocytochemistry) and PGE(2) synthesis (enzyme immunoassay). Inhibition of thrombin by D-Phe-Pro-Arg-chloromethylketone (PPACK) did not significantly reduce PGE(2) synthesis, which remained elevated compared with control. We also investigated the basic fibroblast growth factor (bFGF) dependence of thrombin-induced PGE(2) elevations. Recombinant human bFGF concentration dependently increased PGE(2) synthesis, and a bFGF neutralizing antibody inhibited PGE(2) synthesis induced by TP367 and **TP508** (-40%) and by thrombin (-20%) (but not Cit-NH(2)). Thrombin, therefore, upregulates COX-2-derived PGE(2) synthesis by both catalytic cleavage of PAR(1) and bFGF-dependent noncatalytic activity. This presents a novel mechanism by which intestinal myofibroblasts might regulate epithelial chloride secretion.
ACCESSION NUMBER: 2003163010 EMBASE
TITLE: PAR(1)-dependent and independent increases in COX-2 and PGE(2) in human colonic myofibroblasts stimulated by thrombin.
AUTHOR: Seymour M.L.; Zaidi N.F.; Hollenberg M.D.; MacNaughton W.K.
CORPORATE SOURCE: W.K. MacNaughton, Mucosal Inflammation Research Group, Univ. of Calgary, 3330 Hospital Drive NW, Calgary, Alta. T2N 4N1, Canada. wmacnaug@ucalgary.ca
SOURCE: American Journal of Physiology - Cell Physiology, (1 May 2003) 284/5 53-5 (C1185-C1192).
Refs: 42
ISSN: 0363-6143. CODEN: AJPCDD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
LANGUAGE: English
SUMMARY LANGUAGE: English

L1 ANSWER 41 OF 59 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Controlled release of an osteogenic peptide from injectable biodegradable polymeric composites.
AB Poly(D,L-lactic-co-glycolic acid)/poly(ethylene glycol) (PLGA/PEG) blend microparticles loaded with the osteogenic peptide **TP508** were added to a mixture of poly(propylene fumarate) (PPF), poly(propylene fumarate)-diacrylate (PPF-DA), and sodium chloride (NaCl) for the fabrication of PPF composite scaffolds that could allow for tissue ingrowth as well as for the controlled release of **TP508** when implanted in an orthopedic defect site. In this study, PPF composites were fabricated and the in vitro release kinetics of **TP508** were

determined. **TP508** loading within the PLGA/PEG microparticles, PEG content within the PLGA/PEG microparticles, the microparticle content of the PPF composite polymer component, and the leachable porogen initial mass percent of the PPF composites were varied according to a fractional factorial design and the effect of each variable on the release kinetics was determined for up to 28 days. Each composite formulation released **TP508** with a unique release profile. The initial release (release through day 1) of the PLGA/PEG microparticles was reduced upon inclusion in the PPF composite formulations. Day 1 normalized cumulative mass release from PPF composites ranged from 0.14.+-.0.01 to 0.41.+-.0.01, whereas the release from PLGA/PEG microparticles ranged from 0.31.+-.0.02 to 0.58.+-.0.01. After 28 days, PPF composites released 53.+-.4% to 86.+-.2% of the entrapped peptide resulting in cumulative mass releases ranging from 0.14.+-.0.01 .mu.g **TP508**/mm(3) scaffold to 2.46.+-.0.05 .mu.g **TP508**/mm(3) scaffold. The results presented here demonstrate that PPF composites can be used for the controlled release of **TP508** and that alterations in the composite's composition can lead to modulation of the **TP508** release kinetics. These composites can be used to explore the effects varied release kinetics and dosages on the formation of bone in vivo.

ACCESSION NUMBER: 2002446418 EMBASE
TITLE: Controlled release of an osteogenic peptide from injectable biodegradable polymeric composites.
AUTHOR: Hedberg E.L.; Tang A.; Crowther R.S.; Carney D.H.; Mikos A.G.
CORPORATE SOURCE: A.G. Mikos, Department of Bioengineering, Rice University, MS-142, P.O. Box 1892, Houston, TX 77251-1892, United States. mikos@rice.edu
SOURCE: Journal of Controlled Release, (5 Dec 2002) 84/3 (137-150). Refs: 39
ISSN: 0168-3659 CODEN: JCREEC
PUBLISHER IDENT.: S 0168-3659(02)00261-4
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

L1 ANSWER 42 OF 59 EMBASE
TI Thrombin peptide, **TP508**, stimulates angiogenic responses in animal models of dermal wound healing, in chick chorioallantoic membranes, and in cultured human aortic and microvascular endothelial cells.
AB The .alpha.-thrombin peptide, **TP508**, accelerates the healing of full-thickness wounds in both normal and ischemic skin. In wounds treated with **TP508**, a pattern of increased vascularization is consistently observed both grossly and microscopically when compared to wounds treated with saline. One possible mechanism by which the peptide accelerates wound healing is by promoting revascularization of granulation tissue at the injured site. To evaluate the angiogenic potential of **TP508**, the peptide was tested in the chick embryo chorioallantoic membrane (CAM), where it increased the density and size of CAM blood vessels relative to controls. Additionally, **TP508** stimulated chemokinesis and chemotaxis in a dose-dependent fashion in cultured human aortic and human microvascular endothelial cells. Taken together, these in vivo and in vitro data support an angiogenic role for **TP508** in wound healing. A working model is presented to explain how this 23-amino-acid peptide, which lacks proteolytic activity, is generated during wound healing and contributes to the nonproteolytic functions associated with .alpha.-thrombin during tissue repair.

ACCESSION NUMBER: 2002098497 EMBASE
TITLE: Thrombin peptide, **TP508**, stimulates angiogenic

responses in animal models of dermal wound healing, in chick chorioallantoic membranes, and in cultured human aortic and microvascular endothelial cells.

AUTHOR: Norfleet A.M.; Bergmann J.S.; Carney D.H.

CORPORATE SOURCE: D.H. Carney, Chrysalis BioTechnology, 2200 Market Street, Galveston, TX 77550, United States. dcarney@chrysalisbio.com

SOURCE: General Pharmacology: Vascular System, (2000) 35/5 (249-254).
Refs: 26
ISSN: 0306-3623 CODEN: GEPHDP

PUBLISHER IDENT.: S 0306-3623(01)00118-5

COUNTRY: United States

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 013 Dermatology and Venereology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

L1 ANSWER 43 OF 59 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

TI Thrombin peptide **TP508** accelerates closure of dermal excisions in animal tissue with surgically induced ischemia.

AB **TP508** is a synthetic peptide corresponding to amino acids 508 through 530 of human prothrombin. We previously demonstrated that a Single topical application of **TP508** stimulates revascularization and healing of acute incisional and excisional wounds in normal, healthy rat skin. To determine if **TP508** would enhance wound healing in ischemic skin, we used bipedicle flaps, cranially based flaps, and free grafts to surgically create ischemic regions on the backs of rats. Full-thickness, circular excisions were made within the flaps or grafts and immediately treated with a single application of saline .+-. **TP508** (0.1 .mu.g/wound). Compared to wound closure in normal skin, ischemic skin wounds exhibited delayed closure, and the length of delay correlated with the degree of surgically induced ischemia. **TP508** significantly accelerated closure in both normal and ischemic skin, resulting in closure rates that were increased within the first 7 days of wounding by 30% in normal tissue and bipedicle flaps, 50% in cranially based flaps, and 225% in free grafts. Moreover, in both flap models, **TP508** restored the rate of closure to a rate approximating the control rate observed in normal skin. Histological comparisons of wound tissue from normal skin and cranially based flaps showed that ischemia reduced early recruitment of inflammatory cells at day 1 but increased inflammatory cell numbers in wound beds at day 14. **TP508** treatment of ischemic flap wounds significantly increased early inflammatory cell recruitment and restored the normal rapid resolution of the inflammatory phase. In addition, at day 7, **TP508**-treated wounds appeared to have an increased number of large functional blood vessels compared to saline controls. These studies support the potential efficacy of **TP508** in treating ischemic wounds in humans.

ACCESSION NUMBER: 2001059952 EMBASE

TITLE: Thrombin peptide **TP508** accelerates closure of dermal excisions in animal tissue with surgically induced ischemia.

AUTHOR: Norfleet A.M.; Huang Y.; Sower L.E.; Redin W.R.; Fritz R.R.; Carney D.H.

CORPORATE SOURCE: Dr. D.H. Carney, Dept. of Human Biol. Chem./Genetics, Univ. of Texas Medical Branch, 301 University Blvd., Galveston, TX 77555-0645, United States. dcarney@utmb.edu

SOURCE: Wound Repair and Regeneration, (2000) 8/6 (517-529).
Refs: 33
ISSN: 1067-1927 CODEN: WREREU

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 013 Dermatology and Venereology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L1 ANSWER 44 OF 59 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Acceleration of full-thickness wound healing in normal rats by the synthetic thrombin peptide, **TP508**.
AB Thrombin is an essential factor in hemostasis, inflammation, and tissue repair. The synthetic thrombin peptide, **TP508**, binds to high-affinity thrombin receptors and mimics cellular effects of thrombin at sites of tissue injury. Treatment of full-thickness excisional wounds in normal rats with a single topical application of 0.1 .mu.g **TP508** (14 pmol/cm2) reproducibly accelerates wound closure, yielding wounds that on average close 39% more than controls by day 7 ($p < 0.001$). Wounds treated with 1.0 .mu.g **TP508** are 35% and 43% ($p < 0.001$) smaller than controls on day 7 and 10, respectively. The early rate of closure is .apprx.40% greater in **TP508**-treated than vehicle-treated wounds (20 versus 14 mm2/day) and remains higher through day 7. Breaking strength after closure is slightly greater (15-23%) in wounds treated with **TP508** than with saline alone. Histologic comparisons show that **TP508** enhances recruitment of inflammatory cells to the wound site within 24 hours post- injury. **TP508** treatment also augments revascularization of injured tissue, as evidenced at day 7 by the larger size of functional vessels in the granulation tissue and by the directed development of blood vessels to wounds. These studies raise the possibility that **TP508** may be clinically useful in management of open wounds.
ACCESSION NUMBER: 2000228994 EMBASE
TITLE: Acceleration of full-thickness wound healing in normal rats by the synthetic thrombin peptide, **TP508**.
AUTHOR: Stiernberg J.; Norfleet A.M.; Redin W.R.; Warner W.S.; Fritz R.R.; Carney D.H.
CORPORATE SOURCE: Dr. D.H. Carney, Dept. of Human Biol. Chem./Genetics, University of Texas Medical Branch, 301 University Blvd., Galveston, TX 77555-0645, United States. dcarney@utmb.edu
SOURCE: Wound Repair and Regeneration, (2000) 8/3 (204-215).
Refs: 41
ISSN: 1067-1927 CODEN: WREREU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
013 Dermatology and Venereology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L1 ANSWER 45 OF 59 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Thrombin peptide, **TP508**, induces differential gene expression in fibroblasts through a nonproteolytic activation pathway.
AB Prior studies have shown that synthetic peptides representing the domain of thrombin responsible for high-affinity binding to fibroblasts stimulate chemotactic and cell proliferative signals through a nonproteolytic mechanism. One of these peptides, **TP508**, has recently been shown to be chemotactic for neutrophils, to enhance collagen accumulation in wounds, to enhance revascularization of wounds, and to accelerate the healing of incisional and open wounds in normal animals and in animals with impaired healing. To determine whether **TP508** activates the proteolytically activated receptor for thrombin (PAR1), or the signals that are activated by PAR1, we treated human fibroblasts with **TP508** and the PAR1-activating peptide, SFLLRNP, and analyzed the effects of these peptides on gene expression using differential display reverse transcriptase polymerase chain reaction. **TP508** induces expression of a number of specific message fragments with short tyrosine

kinase-like domains that are not induced by SFLLRNP. Sequencing fulllength clones prepared by Marathon extension of **TP508**-induced fragments. revealed that among the induced transcripts, there was a sequence with 88% homology to human annexin V. Northern analysis with authentic annexin V cDNA confirms that **TP508**, but not SFLLRNP, induces expression of annexin V in human fibroblasts. These results demonstrate that **TP508** activates a cellular response separate from that activated through PAR1 and supports the hypothesis that **TP508** acts through a separate nonproteolytically activated thrombin receptor that may be responsible for high-affinity thrombin binding and for nonproteolytic signals that are required for thrombin stimulation of cell proliferation.

ACCESSION NUMBER: 1999293806 EMBASE
TITLE: Thrombin peptide, **TP508**, induces differential gene expression in fibroblasts through a nonproteolytic activation pathway.
AUTHOR: Sower L.E.; Payne D.A.; Meyers R.; Carney D.H.
CORPORATE SOURCE: D.H. Carney, Dept. of Human Biological Chem./Gen., University of Texas Medical Branch, 301 University Blvd., Galveston, TX 77555-0645, United States. dcarney@marlin.utmb.edu
SOURCE: Experimental Cell Research, (15 Mar 1999) 247/2 (422-431). Refs: 83
ISSN: 0014-4827 CODEN: ECREAL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

L1 ANSWER 46 OF 59 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Renal entactin (nidogen): Isolation, characterization and tissue distribution.
AB Entactin/nidogen (E/N) was isolated from bovine renal tubular basement membrane. Apparent molecular weight, amino acid composition, and molecular configuration by electron microscopy rotary shadowing were similar to that of nidogen from EHS mouse tumor. The identity of bovine E/N was confirmed using a **thrombin derived peptide**, the sequence of which corresponded to a region within mouse and human E/N. Monoclonal and polyclonal anti-E/N antibodies were used to determine the distribution of E/N in human kidney by immunofluorescent and immunoelectron microscopy. E/N was present in all renal basement membranes and was distributed through the full width of the glomerular basement membrane (GBM) with accentuation along its epithelial aspects. E/N distribution was similar to that of novel collagen chain .alpha.3(IV) NC domain in the GBM. In the mesangium, E/N was distributed mainly in the peripheral mesangial region that is bounded by the GBM, while classical collagen chain .alpha.1(IV) NC as present diffusely throughout the mesangium. In the developing nephron, E/N was present in basement membranes of the ureteric bud, primitive vesicle and S-form. In all instances, E/N co-localized with laminin B2 chain. Prominent E/N detection within the mesangium was observed in diseases where mesangial expansion was present. This process was also seen in early diabetic nephropathy, but disappeared with disease progression. However, all thickened diabetic renal basement membranes showed an increase in E/N which was also present in Kimmelstiel-Wilson lesions. E/N was observed in the GBM ''spikes'' of membranous glomerulonephritis and in epithelial crescents associated with various disorders. The association between E/N, laminin and type IV collagen chains observed in the normal kidney were maintained in disorders with altered E/N distribution. We could not detect any changes in the distribution of E/N in other acquired and hereditary kidney diseases. These observations reflect the involvement of E/N in the structure and disease alteration of renal basement membranes and mesangial matrix.

ACCESSION NUMBER: 91332306 EMBASE
DOCUMENT NUMBER: 1991332306

TITLE: Renal entactin (nidogen): Isolation, characterization and tissue distribution.
AUTHOR: Katz A.; Fish A.J.; Kleppel M.M.; Hagen S.G.; Michael A.F.; Butkowski R.J.
CORPORATE SOURCE: University of Minnesota, Medical School, Div. of Pediatric Nephrology, 515 Delaware Street SE,Minneapolis, MN 55455, United States
SOURCE: Kidney International, (1991) 40/4 (643-652).
ISSN: 0085-2538 CODEN: KDYIA5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
028 Urology and Nephrology
LANGUAGE: English
SUMMARY LANGUAGE: English

L1 ANSWER 47 OF 59 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Hormone-like activity of human thrombin.
AB Recently, we have shown that thrombin is a chemotaxin and growth-promoting agent for cells of the mononuclear phagocytic lineage. These activities are independent of thrombin's enzymatic activity. Unlike other chemotactic factors, thrombin is specific for monocytes and does not attract granulocytes. To further explore the cellular specificity we have used a human leukemia cell line HL-60 that is capable of in vitro differentiation toward either monocytes (HL-60/mono) following incubation with 1,25(OH)2D3, or granulocytes (HL-60/gran) following incubation with DMSO. In contrast to undifferentiated HL-60 cells or HL-60/gran, we find that HL-60/mono respond chemotactically to intact human .alpha.-thrombin, esterolytically inactive iPR2P-.alpha.-thrombin, and the **thrombin -derived peptide** CB67-129, previously shown to contain the thrombin chemotactic exosite. In addition, thrombin induces in HL-60/mono association of actin with the cytoskeleton and causes an increase in levels of free cytosolic Ca2+. These phenomena are well characterized as early events occurring concomitant with directed cell movement associated with exposure to chemotactic agents such as FMLP. Furthermore, in contrast to fibroblasts, both iPR2P-.alpha.-thrombin and the thrombin chemotactic peptide CB67-129 evoke dose-dependent [3H]TdR incorporation, protein synthesis, and cell replication in growth-arrested J-744 cells, a murine macrophage-like cell line. Limited tryptic digests of CB67-129 lose chemotactic activity but retain full mitogenic activity, demonstrating that as with PDGF, the sites on CB67-129 required for chemotaxis and mitogenesis are clearly dissociable. The mitogenic effects of the CB67-129 digest can be mimicked by a synthetic tetradecapeptide analogue of CB67-129 (residues 367-380) that includes the loop B insertion sequence, previously shown to be critical for thrombin's chemotactic effects. From these data, it is apparent that the loop B insertion is critical for thrombin's nonenzymic biological effects on cells, but additional sites are required for stimulation of cell movement.
ACCESSION NUMBER: 87090010 EMBASE
DOCUMENT NUMBER: 1987090010
TITLE: Hormone-like activity of human thrombin.
AUTHOR: Bar-Shavit R.; Hruska K.A.; Kahn A.J.; Wilner G.D.
CORPORATE SOURCE: Department of Pathology, Washington University School of Medicine, St. Louis, MO 63110, United States
SOURCE: Annals of the New York Academy of Sciences, (1986) Vol. 485/- (335-348).
CODEN: ANYAA
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
002 Physiology
025 Hematology
LANGUAGE: English

L1 ANSWER 48 OF 59 WPIDS (C) 2003 THOMSON DERWENT
TI Promoting healing of chronic dermal skin ulcer such as diabetic ulcer, on a subject, by contacting the skin ulcer with an agonist of non-proteolytically activated thrombin receptor.
AN 2003-289898 [28] WPIDS
AB WO2003013569 A UPAB: 20030501
NOVELTY - Promoting (M) healing of a chronic dermal skin ulcer on a subject, comprises contacting the chronic dermal skin ulcer with a thrombin peptide derivative.

DETAILED DESCRIPTION - Promoting (M) healing of a chronic dermal skin ulcer on a subject comprises contacting the chronic dermal skin ulcer with a thrombin peptide derivative having the amino acid sequence (S1):

R1-Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-R2 (S1)

R1-Asp-Asn-Met-Phe-Cys-Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-Met-Lys-Ser-Pro-Phe-R2 (S2)

R1 = -H or R3-C(O)-;

R2 = -OH or -NR4R5;

R3 = -H or 1-6C alkyl group; and

R4 and R5 = -H, 1-6C alkyl group or taken together with nitrogen atom to which they are bonded, a non-aromatic heterocyclic group, provided that zero, one, two or three amino acids at positions 1-9 and 14-23 in the thrombin peptide derivative differ from the amino acid at the corresponding position of (S1), or positions 1-14 and 19-33 of the thrombin peptide derivative differ from the amino acid at the corresponding position of (S2), an N-terminal truncated fragment of the thrombin peptide derivative having at least 14 amino acids or a C-terminal truncated fragment of the thrombin peptide derivative having at least 18 amino acids.

ACTIVITY - Antiulcer.

A multi-center, randomized, double blind, three-arm Phase IIa pilot study evaluating synthetic thrombin peptide **TP508** for accelerating the healing of chronic diabetic ulcers was designed. Patients were randomized to one of three topical treatment groups: 1 micro g of **TP508** in saline applied twice weekly, 10 micro g of **TP508** in saline applied twice weekly, or saline placebo applied twice weekly. All patients received a regiment of standard diabetic ulcer care consisting of initial sharp debridement, wound cleansing, wound dressing and wound pressure off loading. Wounds were evaluated twice a week for 20 weeks or until wound closure. Blood chemistry and hematology tests were performed at patient enrollment, and at weeks 5, 10, 15 and 20. A radiographic assessment was conducted every 5 weeks to study effects on underlying bone composition. The primary efficacy endpoint was the proportion of patients that achieve full wound closure. Full wound closure was defined as 100% epithelialization, with no drainage and no infection, as determined by visual inspection by the clinician. Three different patient analysis groups were defined to better study the efficacy endpoints. The intent-to-treat (ITT) group included all 60 patients receiving study drug and was primarily used for safety evaluation. The per-protocol (PP) group included 40 patients that met a predefined set of criteria meant to assure the highest compliance with the protocol. The efficacy group included 46 patients which met standards that were chosen prior to unblinding to be most relevant to allow an accurate evaluation of wound healing. Primary endpoint results were described for each patient group. The primary efficacy endpoint results showed a dose response relationship for 100% closure in all populations examined, with 1 micro g treatments resulting in 4-15% more closure than saline placebo controls, and 10 micro g treatments resulting in 13-24% more closure than saline placebo controls. Specifically, in the PP treatment group, 5 of 15 or 33% healed in the saline placebo group, 5 of 11 or 45% healed in 1 micro g treatment group, and 8 of 14 or 57% healed in the 10 micro g group. In the efficacy (EF) group selected to include wounds slightly smaller and slightly larger than those in the stricter per protocol group, this trend

was again seen with 38% healing in the placebo group, 53% healing in the 1 mu g group, and 60% healing in the 10 micro g group. The difference was again noted in the ITT population, although the percentage that healed in the saline placebo group was larger (48%) because this group included several small and superficial wounds that healed, but did not meet protocol to be defined as chronic diabetic wounds for the study. These results compared favorably to clinical trials for Regranex (RTM), where data compiled from 4 controlled randomized clinical trials showed that 83 of 254 or 33% of the vehicle placebo wounds healed by 20 weeks and 122 of 285 or 43% of the Regranex (RTM)-treated wounds healed by 20 weeks. These results showed an increased percentage of ulcer closure for patients treated with **TP508** and indicated median healing times that reflected a faster rate of healing.

MECHANISM OF ACTION - Agonist of non-proteolytically activated thrombin receptor.

USE - (M) is useful for promoting healing of a chronic dermal skin ulcer, especially diabetic ulcer, decubitus ulcer, venous stasis ulcer or arterial ulcer, on a companion animal, farm animal or laboratory animal (claimed).

Dwg.0/0

ACCESSION NUMBER: 2003-289898 [28] WPIDS
DOC. NO. CPI: C2003-075228
TITLE: Promoting healing of chronic dermal skin ulcer such as diabetic ulcer, on a subject, by contacting the skin ulcer with an agonist of non-proteolytically activated thrombin receptor.
DERWENT CLASS: B04 B05
INVENTOR(S): CARNEY, D H
PATENT ASSIGNEE(S): (TEXA) UNIV TEXAS SYSTEM
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003013569	A2	20030220	(200328)*	EN	19

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003013569	A2	WO 2002-US1151	20020116

PRIORITY APPLN. INFO: US 2001-308198P 20010727

L1 ANSWER 49 OF 59 WPIDS (C) 2003 THOMSON DERWENT
TI Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor.
AN 2002-303796 [34] WPIDS
AB WO 200205836 A UPAB: 20020528
NOVELTY - Stimulating (M) bone growth at a site in a subject in need of osteoinduction, involves administering to the site, an agonist (I) of the non-proteolytically activated thrombin receptor.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a pharmaceutical composition (PC) comprising an implantable, biocompatible carrier and (I).

ACTIVITY - Osteopathic.

MECHANISM OF ACTION - Stimulator of bone growth; agonist of activated thrombin receptor

12.5 cm segmental defect was created in each ulna of 20 male New Zealand rabbits. The bilateral ulnar osteotomies were created exactly the same size by using a small metal guide to direct the cutting blade of the oscillating microsaw. Each rabbit acted as its own control, thus the left defect was filled with microspheres not containing **TP508**, while the right defect was filled with microspheres containing 100 or 200 micro g **Tp508** (10 animals/group). Rabbits given bilateral ulnar osteomies were randomly divided into two groups. The first group received 100 micro g of **TP508** in microspheres (30 mg) in the right limb and microspheres alone in the left limb. The second group was treated similarly, but received 200 mu g of **TP508**. Animals were X-rayed at 2-week intervals, beginning at week 3, and sacrificed at 9 weeks. 100 micro g of **TP508** stimulated mineralization in the defect at 3 and 5 weeks post-surgery. X-rays at 7 and 9 weeks appeared similar to those obtained at 5 weeks. Animals were sacrificed at 9 weeks post-surgery and the ulna-radius was removed and photographed. In most cases a large defect was visible in ulnas from the control limbs, in contrast with the **TP508**-treated limbs, in which most of the defects were successfully closed. After sacrifice at 9 weeks post-surgery, repair strength was measured by torsion testing. The results showed that at 100 micro g, **TP508** more than doubled the mechanical strength of the healing defect as measured by all the parameters tested. Even stronger repairs were noted in the 200 micro g group, with most parameters being approximately 50% higher than those seen in the low dose treatment group.

USE - (M) is useful for stimulating bone growth at a site in a subject (e.g. a farm animal, companion animal or laboratory animal), in need of osteoinduction, such as the site in need of a bone graft in a subject, a segmental bone gap, a bone void or a non-union fracture (claimed).

Dwg.0/0

ACCESSION NUMBER: 2002-303796 [34] WPIDS
DOC. NO. CPI: C2002-088279
TITLE: Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor.
DERWENT CLASS: A96 B04
INVENTOR(S): CARNEY, D H; CROWTHER, R S; REDIN, W R; SIMMONS, D J; YANG, J
PATENT ASSIGNEE(S): (TEXA) UNIV TEXAS SYSTEM
COUNTRY COUNT: 97
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002005836	A2	20020124	(200234)*	EN	27
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001076977	A	20020130	(200236)		
US 2002128202	A1	20020912	(200262)		
US 2002182205	A1	20021205	(200301)		
EP 1301196	A2	20030416	(200328)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2002005836	A2		WO 2001-US22641	20010718
AU 2001076977	A		AU 2001-76977	20010718
US 2002128202	A1	Provisional	US 2000-219300P	20000719
			US 2001-909122	20010719
US 2002182205	A1	Provisional	US 2000-219300P	20000719
		Cont of	US 2001-909122	20010719
			US 2002-50692	20020116
EP 1301196	A2		EP 2001-954752	20010718
			WO 2001-US22641	20010718

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001076977	A	Based on	WO 200205836
EP 1301196	A2	Based on	WO 200205836

PRIORITY APPLN. INFO: US 2000-219300P 20000719; US 2001-909122 20010719; US 2002-50692 20020116

L1 ANSWER 50 OF 59 WPIDS (C) 2003 THOMSON DERWENT

TI Promoting cardiac tissue repair, stimulating revascularization, stimulating vascular endothelial cell proliferation, and inhibiting vascular occlusion by using angiogenic thrombin derivative peptide.

AN 2002-179665 [23] WPIDS

AB WO 200204008 A UPAB: 20020411

NOVELTY - Promoting cardiac tissue repair or stimulating revascularization, stimulating vascular endothelial cell proliferation, inhibiting restenosis in a patient following balloon angioplasty, and for inhibiting vascular occlusion in a patient by administering an angiogenic thrombin derivative peptide (I) to cardiac tissue or blood vessels.

ACTIVITY - Vasotropic; cardiant.

(I) was tested for vasotropic and cardiant activity. Yucatan minipigs had toroid shaped ameroid occluders placed on their proximal left circumflex arteries. The ameroid imbibed water over time, causing constriction of the vessel. Occlusion was verified four weeks after surgery by contrast enhanced angiography. At that time, each animal's chest was reopened, where upon the region of ischemia was injected with a slow release formulation of **TP508** (100 micro l, i.e., **TP508**-containing poly(D,L-lactide-co-glycolide) (PLGA) microspheres, suspended in a Pluronic gel, into 10 sites (100 micro l/site) in the ischemic area. Controls received PLGA microspheres in Pluronic gel without **TP508**. Baseline, and post-treatment angiograms and echocardiograms were obtained. Indices for myocardial wall thickening and cardiac ejection fraction showed trends that **TP508** treated animals tolerated dobutamine-induced stress better than controls. After 3 weeks, the animals were evaluated with contrast enhanced echocardiography. Initial results on this limited number of animals demonstrated that **TP508** treated animals under dobutamine stress had a slightly larger increase in ejection fraction and better maintained wall thickening compared to controls. Thus, this treatment appears to help restore functionality to the ischemic heart muscle.

MECHANISM OF ACTION - Angiogenic proliferation and endothelial cells migration inducer.

USE - The method utilizing (I) is useful for promoting cardiac tissue repair, stimulating revascularization, stimulating vascular endothelial cell proliferation, inhibiting restenosis in a patient following balloon angioplasty, and for inhibiting vascular occlusion in a patient (claimed).

Dwg.0/3

ACCESSION NUMBER: 2002-179665 [23] WPIDS

DOC. NO. CPI: C2002-055805

TITLE: Promoting cardiac tissue repair, stimulating

revascularization, stimulating vascular endothelial cell proliferation, and inhibiting vascular occlusion by using angiogenic thrombin derivative peptide.
DERWENT CLASS: B04 B07 D22
INVENTOR(S): CARNEY, D H
PATENT ASSIGNEE(S): (TEXA) UNIV TEXAS SYSTEM
COUNTRY COUNT: 97
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002004008	A2	20020117	(200223)*	EN	24
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001078907	A	20020121	(200234)		
US 2002061852	A1	20020523	(200239)		
EP 1253937	A2	20021106	(200281)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 2002187933	A1	20021212	(200301)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2002004008	A2		WO 2001-US21944	20010712
AU 2001078907	A		AU 2001-78907	20010712
US 2002061852	A1	Provisional	US 2000-217583P	20000712
			US 2001-904090	20010712
EP 1253937	A2		EP 2001-957136	20010712
			WO 2001-US21944	20010712
US 2002187933	A1	Provisional	US 2000-217583P	20000712
		Cont of	US 2001-904090	20010712
			US 2002-50611	20020116

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001078907	A	Based on	WO 200204008
EP 1253937	A2	Based on	WO 200204008

PRIORITY APPLN. INFO: US 2000-217583P 20000712; US 2001-904090 20010712; US 2002-50611 20020116

=> s TP508
L10 47 TP508

=> d l10 ti abs ibib tot

L10 ANSWER 1 OF 47 MEDLINE
TI PAR1-dependent and independent increases in COX-2 and PGE2 in human colonic myofibroblasts stimulated by thrombin.
AB Subepithelial myofibroblast-derived prostaglandin E(2) (PGE(2)) regulates epithelial chloride secretion in the intestine. Thrombin is elevated in inflammatory conditions of the bowel. Therefore, we sought to determine a role for thrombin in regulating PGE(2) synthesis by colonic myofibroblasts. Incubation of cultured CCD-18Co colonic myofibroblasts with thrombin, the proteinase-activated receptor 1 (PAR(1))-activating

peptide (Cit-NH(2)), and peptides corresponding to 2 noncatalytic regions of thrombin (TP367 and **TP508**) for 18 h increased both cyclooxygenase (COX)-2 expression (immunocytochemistry) and PGE(2) synthesis (enzyme immunoassay). Inhibition of thrombin by D-Phe-Pro-Arg-chloromethylketone (PPACK) did not significantly reduce PGE(2) synthesis, which remained elevated compared with control. We also investigated the basic fibroblast growth factor (bFGF) dependence of thrombin-induced PGE(2) elevations. Recombinant human bFGF concentration dependently increased PGE(2) synthesis, and a bFGF neutralizing antibody inhibited PGE(2) synthesis induced by TP367 and **TP508** (approximately 40%) and by thrombin (approximately 20%) (but not Cit-NH(2)). Thrombin, therefore, upregulates COX-2-derived PGE(2) synthesis by both catalytic cleavage of PAR(1) and bFGF-dependent noncatalytic activity. This presents a novel mechanism by which intestinal myofibroblasts might regulate epithelial chloride secretion.

ACCESSION NUMBER: 2003159038 MEDLINE
DOCUMENT NUMBER: 22562466 PubMed ID: 12505789
TITLE: PAR1-dependent and independent increases in COX-2 and PGE2 in human colonic myofibroblasts stimulated by thrombin.
AUTHOR: Seymour Michelle L; Zaidi Nosheen F; Hollenberg Morley D; MacNaughton Wallace K
CORPORATE SOURCE: Mucosal Inflammation Research Group, University of Calgary, Calgary, Alberta, Canada T2N 4N1.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY. CELL PHYSIOLOGY, (2003 May) 284 (5) C1185-92.
Journal code: 100901225. ISSN: 0363-6143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030406
Last Updated on STN: 20030522
Entered Medline: 20030521

L10 ANSWER 2 OF 47 MEDLINE
TI Controlled release of an osteogenic peptide from injectable biodegradable polymeric composites.
AB Poly(D,L-lactic-co-glycolic acid)/poly(ethylene glycol) (PLGA/PEG) blend microparticles loaded with the osteogenic peptide **TP508** were added to a mixture of poly(propylene fumarate) (PPF), poly(propylene fumarate)-diacrylate (PPF-DA), and sodium chloride (NaCl) for the fabrication of PPF composite scaffolds that could allow for tissue ingrowth as well as for the controlled release of **TP508** when implanted in an orthopedic defect site. In this study, PPF composites were fabricated and the in vitro release kinetics of **TP508** were determined. **TP508** loading within the PLGA/PEG microparticles, PEG content within the PLGA/PEG microparticles, the microparticle content of the PPF composite polymer component, and the leachable porogen initial mass percent of the PPF composites were varied according to a fractional factorial design and the effect of each variable on the release kinetics was determined for up to 28 days. Each composite formulation released **TP508** with a unique release profile. The initial release (release through day 1) of the PLGA/PEG microparticles was reduced upon inclusion in the PPF composite formulations. Day 1 normalized cumulative mass release from PPF composites ranged from 0.14+/-0.01 to 0.41+/-0.01, whereas the release from PLGA/PEG microparticles ranged from 0.31+/-0.02 to 0.58+/-0.01. After 28 days, PPF composites released 53+/-4% to 86+/-2% of the entrapped peptide resulting in cumulative mass releases ranging from 0.14+/-0.01 microg **TP508**/mm(3) scaffold to 2.46+/-0.05 microg **TP508**/mm(3) scaffold. The results presented here demonstrate that PPF composites can be used for the controlled release of **TP508** and that alterations in the composite's composition can lead to modulation of the **TP508** release kinetics. These composites

can be used to explore the effects varied release kinetics and dosages on the formation of bone in vivo.

ACCESSION NUMBER: 2003004378 IN-PROCESS
DOCUMENT NUMBER: 22356120 PubMed ID: 12468217
TITLE: Controlled release of an osteogenic peptide from injectable biodegradable polymeric composites.
AUTHOR: Hedberg Elizabeth L; Tang Andrew; Crowther Roger S; Carney Darrell H; Mikos Antonios G
CORPORATE SOURCE: Department of Bioengineering, Rice University, PO Box 1892, MS-142, Houston, TX 77251-1892, USA.
CONTRACT NUMBER: R01-AR44381 (NIAMS)
R01-DE13031 (NIDCR)
T32-GM08362 (NIGMS)
SOURCE: JOURNAL OF CONTROLLED RELEASE, (2002 Dec 5) 84 (3) 137-50. Journal code: 8607908. ISSN: 0168-3659.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030105
Last Updated on STN: 20030105

L10 ANSWER 3 OF 47 MEDLINE
TI Effects of thrombin peptides on wound healing and proliferation and migration of normal human epidermal keratinocyte (NHEK).
AB OBJECTIVE: To define the effects of thrombin peptides on wound healing and NHEK proliferation and migration. METHODS: A wound model was made with four 1.5 cm circular full thickness dermal excisions on the back of each Sprague-Dawley rat. 0.1 microgram (40 microliter) **TP508** was applied to each circular excisional wound in 9 rats, the other 9 received saline only. Wound area was calculated with JAVA Jandel and IMAGE PRO software. NHEK945 proliferation was assessed by MTT assay and direct cell count with a Coulter Counter. Cell migration was determined by 48-well Boyden Chamber. Cells migrated onto the lower surface of the filter were assessed by a Chemi Imager 4000 Image Analyzer and expressed as spot density. RESULTS: Wound area in rats treated with **TP508** was 73.7% and 45.4% of saline control on day 7 and 14, respectively. NHEK945 proliferation was accelerated after adding thrombin and **TP508**. The spot density of migrated cells was 76.7 plus minus 13.8 in medium alone. After adding 1 microgram/ml of thrombin and 10 microgram/ml of **TP508**, the spot density was 104.4 plus minus 12.2 and 109.4 plus minus 14.6, respectively. CONCLUSION: Results of this study suggest that both thrombin and **TP508** have significant actions on wound healing and NHEK proliferation and migration, which is important in wound repair.

ACCESSION NUMBER: 2002344571 MEDLINE
DOCUMENT NUMBER: 21866780 PubMed ID: 11876838
TITLE: Effects of thrombin peptides on wound healing and proliferation and migration of normal human epidermal keratinocyte (NHEK).
AUTHOR: Huang Y; Yang Z; Carney D
CORPORATE SOURCE: Institute of Burn Research, Southwestern Hospital, Third Military Medical University, Chongqing 400038.
SOURCE: Zhonghua Shao Shang Za Zhi, (2000 Feb) 16 (1) 26-9. Journal code: 100959418. ISSN: 1009-2587.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020629
Last Updated on STN: 20020713
Entered Medline: 20020712

L10 ANSWER 4 OF 47 MEDLINE

TI Thrombin peptide, **TP508**, stimulates angiogenic responses in animal models of dermal wound healing, in chick chorioallantoic membranes, and in cultured human aortic and microvascular endothelial cells.

AB The alpha-thrombin peptide, **TP508**, accelerates the healing of full-thickness wounds in both normal and ischemic skin. In wounds treated with **TP508**, a pattern of increased vascularization is consistently observed both grossly and microscopically when compared to wounds treated with saline. One possible mechanism by which the peptide accelerates wound healing is by promoting revascularization of granulation tissue at the injured site. To evaluate the angiogenic potential of **TP508**, the peptide was tested in the chick embryo chorioallantoic membrane (CAM), where it increased the density and size of CAM blood vessels relative to controls. Additionally, **TP508** stimulated chemokinesis and chemotaxis in a dose-dependent fashion in cultured human aortic and human microvascular endothelial cells. Taken together, these in vivo and in vitro data support an angiogenic role for **TP508** in wound healing. A working model is presented to explain how this 23-amino-acid peptide, which lacks proteolytic activity, is generated during wound healing and contributes to the nonproteolytic functions associated with alpha-thrombin during tissue repair.

ACCESSION NUMBER: 2002157334 MEDLINE
DOCUMENT NUMBER: 21886336 PubMed ID: 11888680
TITLE: Thrombin peptide, **TP508**, stimulates angiogenic responses in animal models of dermal wound healing, in chick chorioallantoic membranes, and in cultured human aortic and microvascular endothelial cells.
AUTHOR: Norfleet A M; Bergmann J S; Carney D H
CORPORATE SOURCE: Chrysalis BioTechnology, Inc., 2200 Market Street, Suite 600, Galveston, TX 77550, USA.
SOURCE: GENERAL PHARMACOLOGY, (2000 Nov) 35 (5) 249-54. Ref: 26
Journal code: 7602417. ISSN: 0306-3623.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020313
Last Updated on STN: 20020620
Entered Medline: 20020619

L10 ANSWER 5 OF 47 MEDLINE

TI An experimental study of the effects of thrombin receptor activating peptide (**TP508**) on healing of ischemic wound and flap survival in rats.

AB OBJECTIVE: To investigate the effects of the thrombin receptor activating peptide (**TP508**) on healing of ischemic wound and flap survival in rats. METHODS: Sixty-six Sprague-Dawley rats were employed as the model. On the back of the rats, three kinds of wound and flap were made to establish four groups as follows: partial ischemic wound in 16, full ischemic wound in 16, routine wound in 18 and flap in 16 rats. Each group was further divided into **TP508** treating group and isotonic saline control group. The total and necrotic areas of the wounds and flaps were daplicated on acetate papers and calculated with a computer on the 3rd, 7th, 10th and 14th post-operation days (PODs). RESULTS: In routine wounds, the ischemic wound area treated by **TP508** was 73.7% and 45.4% in saline control groups on 7 and 14 (PODs), respectively. While in the flap model, the necrotic flap area treated by **TP508** was 80.4% and 56.8% in control groups on 7 and 14 (PODs), respectively. CONCLUSION: **TP508** could accelerate healing of ischemic wound and improve flap survival in rats.

ACCESSION NUMBER: 2002125188 MEDLINE
DOCUMENT NUMBER: 21849128 PubMed ID: 11859609
TITLE: An experimental study of the effects of thrombin receptor activating peptide (**TP508**) on healing of ischemic wound and flap survival in rats.
AUTHOR: Huang Y; Yang Z; Li A
CORPORATE SOURCE: Institute of Burn Research, Southwestern Hospital, Third Military Medical University, Chongqing 400038, P. R. China.
SOURCE: Zhonghua Shao Shang Za Zhi, (2001 Dec) 17 (6) 339-41. Journal code: 100959418. ISSN: 1009-2587.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020226
Last Updated on STN: 20020508
Entered Medline: 20020507

L10 ANSWER 6 OF 47 MEDLINE
TI Thrombin peptide **TP508** accelerates closure of dermal excisions in animal tissue with surgically induced ischemia.
AB **TP508** is a synthetic peptide corresponding to amino acids 508 through 530 of human prothrombin. We previously demonstrated that a single topical application of **TP508** stimulates revascularization and healing of acute incisional and excisional wounds in normal, healthy rat skin. To determine if **TP508** would enhance wound healing in ischemic skin, we used bipedicle flaps, cranially based flaps, and free grafts to surgically create ischemic regions on the backs of rats. Full-thickness, circular excisions were made within the flaps or grafts and immediately treated with a single application of saline +/- **TP508** (0.1 microg/wound). Compared to wound closure in normal skin, ischemic skin wounds exhibited delayed closure, and the length of delay correlated with the degree of surgically induced ischemia. **TP508** significantly accelerated closure in both normal and ischemic skin, resulting in closure rates that were increased within the first 7 days of wounding by 30% in normal tissue and bipedicle flaps, 50% in cranially based flaps, and 225% in free grafts. Moreover, in both flap models, **TP508** restored the rate of closure to a rate approximating the control rate observed in normal skin. Histological comparisons of wound tissue from normal skin and cranially based flaps showed that ischemia reduced early recruitment of inflammatory cells at day 1 but increased inflammatory cell numbers in wound beds at day 14. **TP508** treatment of ischemic flap wounds significantly increased early inflammatory cell recruitment and restored the normal rapid resolution of the inflammatory phase. In addition, at day 7, **TP508**-treated wounds appeared to have an increased number of large functional blood vessels compared to saline controls. These studies support the potential efficacy of **TP508** in treating ischemic wounds in humans.
ACCESSION NUMBER: 2001285509 MEDLINE
DOCUMENT NUMBER: 21221250 PubMed ID: 11208179
TITLE: Thrombin peptide **TP508** accelerates closure of dermal excisions in animal tissue with surgically induced ischemia.
AUTHOR: Norfleet A M; Huang Y; Sower L E; Redin W R; Fritz R R; Carney D H
CORPORATE SOURCE: Department of Human Biological Chemistry and Genetics, The University of Texas Medical Branch, 301 University Blvd., Galveston, TX 77555-0645, USA.
CONTRACT NUMBER: R44 DK53580 (NIDDK)
SOURCE: WOUND REPAIR AND REGENERATION, (2000 Nov-Dec) 8 (6) 517-29. Journal code: 9310939. ISSN: 1067-1927.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010702
Last Updated on STN: 20010702
Entered Medline: 20010628

L10 ANSWER 7 OF 47 MEDLINE
TI Acceleration of full-thickness wound healing in normal rats by the synthetic thrombin peptide, **TP508**.
AB Thrombin is an essential factor in hemostasis, inflammation, and tissue repair. The synthetic thrombin peptide, **TP508**, binds to high-affinity thrombin receptors and mimics cellular effects of thrombin at sites of tissue injury. Treatment of full-thickness excisional wounds in normal rats with a single topical application of 0.1 microg **TP508** (14 pmol/cm2) reproducibly accelerates wound closure, yielding wounds that on average close 39% more than controls by day 7 ($p < 0.001$). Wounds treated with 1.0 microg **TP508** are 35% and 43% ($p < 0.001$) smaller than controls on day 7 and 10, respectively. The early rate of closure is approximately 40% greater in **TP508**-treated than vehicle-treated wounds (20 versus 14 mm2/day) and remains higher through day 7. Breaking strength after closure is slightly greater (15-23%) in wounds treated with **TP508** than with saline alone. Histologic comparisons show that **TP508** enhances recruitment of inflammatory cells to the wound site within 24 hours post-injury. **TP508** treatment also augments revascularization of injured tissue, as evidenced at day 7 by the larger size of functional vessels in the granulation tissue and by the directed development of blood vessels to wounds. These studies raise the possibility that **TP508** may be clinically useful in management of open wounds.
ACCESSION NUMBER: 2000402971 MEDLINE
DOCUMENT NUMBER: 20345355 PubMed ID: 10886811
TITLE: Acceleration of full-thickness wound healing in normal rats by the synthetic thrombin peptide, **TP508**.
AUTHOR: Stiernberg J; Norfleet A M; Redin W R; Warner W S; Fritz R R; Carney D H
CORPORATE SOURCE: Department of Human Biological Chemistry and Genetics,The University of Texas Medical Branch, Galveston, Texas 77555-0645, USA.
CONTRACT NUMBER: DK-25807 (NIDDK)
GM-475472 (NIGMS)
SOURCE: WOUND REPAIR AND REGENERATION, (2000 May-Jun) 8 (3) 204-15. Journal code: 9310939. ISSN: 1067-1927.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000901
Last Updated on STN: 20000901
Entered Medline: 20000821

L10 ANSWER 8 OF 47 MEDLINE
TI Thrombin peptide, **TP508**, induces differential gene expression in fibroblasts through a nonproteolytic activation pathway.
AB Prior studies have shown that synthetic peptides representing the domain of thrombin responsible for high-affinity binding to fibroblasts stimulate chemotactic and cell proliferative signals through a nonproteolytic mechanism. One of these peptides, **TP508**, has recently been shown to be chemotactic for neutrophils, to enhance collagen accumulation in wounds, to enhance revascularization of wounds, and to accelerate the healing of incisional and open wounds in normal animals and in animals with impaired healing. To determine whether **TP508** activates the

proteolytically activated receptor for thrombin (PAR1), or the signals that are activated by PAR1, we treated human fibroblasts with **TP508** and the PAR1-activating peptide, SFLLRNP, and analyzed the effects of these peptides on gene expression using differential display reverse transcriptase polymerase chain reaction. **TP508** induces expression of a number of specific message fragments with short tyrosine kinase-like domains that are not induced by SFLLRNP. Sequencing full-length clones prepared by Marathon extension of **TP508** -induced fragments revealed that among the induced transcripts, there was a sequence with 88% homology to human annexin V. Northern analysis with authentic annexin V cDNA confirms that **TP508**, but not SFLLRNP, induces expression of annexin V in human fibroblasts. These results demonstrate that **TP508** activates a cellular response separate from that activated through PAR1 and supports the hypothesis that **TP508** acts through a separate nonproteolytically activated thrombin receptor that may be responsible for high-affinity thrombin binding and for nonproteolytic signals that are required for thrombin stimulation of cell proliferation.

ACCESSION NUMBER: 1999167419 MEDLINE
DOCUMENT NUMBER: 99167419 PubMed ID: 10066370
TITLE: Thrombin peptide, **TP508**, induces differential gene expression in fibroblasts through a nonproteolytic activation pathway.
AUTHOR: Sower L E; Payne D A; Meyers R; Carney D H
CORPORATE SOURCE: The Department of Human Biological Chemistry and Genetics, The University of Texas Medical Branch, Galveston, Texas, 77555-0645, USA.
CONTRACT NUMBER: 5RO1 GM47572 (NIGMS)
SOURCE: EXPERIMENTAL CELL RESEARCH, (1999 Mar 15) 247 (2) 422-31. Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990413

L10 ANSWER 9 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Purification and characterization of the high affinity non-proteolytically activated (NPAR) thrombin receptor.
ACCESSION NUMBER: 2003:156453 BIOSIS
DOCUMENT NUMBER: PREV200300156453
TITLE: Purification and characterization of the high affinity non-proteolytically activated (NPAR) thrombin receptor.
AUTHOR(S): Bergmann, J. S. (1); Laird, A. C.; Tsulaia, T. V.; Keherly, M. J.; Carney, D. H.
CORPORATE SOURCE: (1) Human Biological Chemistry and Genetics, Medical Branch, University Texas, Galveston, TX, USA USA
SOURCE: Molecular Biology of the Cell, (Nov. 2002, 2002) Vol. 13, No. Supplement, pp. 290a. print.
Meeting Info.: 42nd Annual Meeting of the American Society for Cell Biology San Francisco, CA, USA December 14-18, 2002 American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 10 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Controlled release of an osteogenic peptide from injectable biodegradable polymeric composites.
AB Poly(D,L-lactic-co-glycolic acid)/poly(ethylene glycol) (PLGA/PEG) blend

microparticles loaded with the osteogenic peptide **TP508** were added to a mixture of poly(propylene fumarate) (PPF), poly(propylene fumarate)-diacrylate (PPF-DA), and sodium chloride (NaCl) for the fabrication of PPF composite scaffolds that could allow for tissue ingrowth as well as for the controlled release of **TP508** when implanted in an orthopedic defect site. In this study, PPF composites were fabricated and the in vitro release kinetics of **TP508** were determined. **TP508** loading within the PLGA/PEG microparticles, PEG content within the PLGA/PEG microparticles, the microparticle content of the PPF composite polymer component, and the leachable porogen initial mass percent of the PPF composites were varied according to a fractional factorial design and the effect of each variable on the release kinetics was determined for up to 28 days. Each composite formulation released **TP508** with a unique release profile. The initial release (release through day 1) of the PLGA/PEG microparticles was reduced upon inclusion in the PPF composite formulations. Day 1 normalized cumulative mass release from PPF composites ranged from 0.14+-0.01 to 0.41+-0.01, whereas the release from PLGA/PEG microparticles ranged from 0.31+-0.02 to 0.58+-0.01. After 28 days, PPF composites released 53+-4% to 86+-2% of the entrapped peptide resulting in cumulative mass releases ranging from 0.14+-0.01 mug **TP508**/mm3 scaffold to 2.46+-0.05 mug **TP508**/mm3 scaffold. The results presented here demonstrate that PPF composites can be used for the controlled release of **TP508** and that alterations in the composite's composition can lead to modulation of the **TP508** release kinetics. These composites can be used to explore the effects varied release kinetics and dosages on the formation of bone in vivo.

ACCESSION NUMBER: 2003:121275 BIOSIS
DOCUMENT NUMBER: PREV200300121275
TITLE: Controlled release of an osteogenic peptide from injectable biodegradable polymeric composites.
AUTHOR(S): Hedberg, Elizabeth L.; Tang, Andrew; Crowther, Roger S.; Carney, Darrell H.; Mikos, Antonios G. (1)
CORPORATE SOURCE: (1) Department of Bioengineering, Rice University, P.O. Box 1892, MS-142, Houston, TX, 77251-1892, USA: mikos@rice.edu USA
SOURCE: Journal of Controlled Release, (5 December 2002) Vol. 84, No. 3, pp. 137-150. print.
ISSN: 0168-3659.
DOCUMENT TYPE: Article
LANGUAGE: English

L10 ANSWER 11 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Thrombin peptide, **TP508**, stimulates angiogenic responses in animal models of dermal wound healing, in chick chorioallantoic membranes, and in cultured human aortic and microvascular endothelial cells.
AB The alpha-thrombin peptide, **TP508**, accelerates the healing of full-thickness wounds in both normal and ischemic skin. In wounds treated with **TP508**, a pattern of increased vascularization is consistently observed both grossly and microscopically when compared to wounds treated with saline. One possible mechanism by which the peptide accelerates wound healing is by promoting revascularization of granulation tissue at the injured site. To evaluate the angiogenic potential of **TP508**, the peptide was tested in the chick embryo chorioallantoic membrane (CAM), where it increased the density and size of CAM blood vessels relative to controls. Additionally, **TP508** stimulated chemokinesis and chemotaxis in a dose-dependent fashion in cultured human aortic and human microvascular endothelial cells. Taken together, these in vivo and in vitro data support an angiogenic role for **TP508** in wound healing. A working model is presented to explain how this 23-amino-acid peptide, which lacks proteolytic activity, is generated during wound healing and contributes to the nonproteolytic functions associated with alpha-thrombin during tissue repair.
ACCESSION NUMBER: 2002:308356 BIOSIS

DOCUMENT NUMBER: PREV200200308356
TITLE: Thrombin peptide, **TP508**, stimulates angiogenic responses in animal models of dermal wound healing, in chick chorioallantoic membranes, and in cultured human aortic and microvascular endothelial cells.
AUTHOR(S): Norfleet, Andrea M.; Bergmann, John S.; Carney, Darrell H. (1)
CORPORATE SOURCE: (1) Chrysalis Bio Technology, 2200 Market Street, Suite 600, Galveston, TX, 77550: dcarney@chrysalisbio.com USA
SOURCE: General Pharmacology, (November, 2000) Vol. 35, No. 5, pp. 249-254. http://www.elsevier.com/locate/genpharm. print. ISSN: 0306-3623.
DOCUMENT TYPE: Article
LANGUAGE: English

L10 ANSWER 12 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI The thrombin peptide **TP508** is a potent chemotactic agent for human neutrophils (PMNs.
ACCESSION NUMBER: 2002:177832 BIOSIS
DOCUMENT NUMBER: PREV200200177832
TITLE: The thrombin peptide **TP508** is a potent chemotactic agent for human neutrophils (PMNs.
AUTHOR(S): Moller, Malinda L. (1); Keherly, Michael J. (1); Carney, Darrell H. (1)
CORPORATE SOURCE: (1) Chrysalis BioTechnology, Inc., 2200 Market, Suite 600, Galveston, TX, 77550 USA
SOURCE: Molecular Biology of the Cell, (Nov, 2001) Vol. 12, No. Supplement, pp. 257a. http://www.molbiolcell.org/. print. Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology Washington DC, USA December 08-12, 2001 ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 13 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Thrombin peptide **TP508** (Chrysalin(R)) upregulates cytokines IL-2, IL-6, and IL-12 in pre-activated peripheral blood mononuclear cells.
ACCESSION NUMBER: 2002:177823 BIOSIS
DOCUMENT NUMBER: PREV200200177823
TITLE: Thrombin peptide **TP508** (Chrysalin(R)) upregulates cytokines IL-2, IL-6, and IL-12 in pre-activated peripheral blood mononuclear cells.
AUTHOR(S): Naldini, Antonella (1); Carney, Darrell H.; Pucci, Annalisa (1); Carraro, Fabio (1)
CORPORATE SOURCE: (1) Institute of General Physiology, University of Siena, Via Aldo Moro, 5, Siena, 53100 Italy
SOURCE: Molecular Biology of the Cell, (Nov, 2001) Vol. 12, No. Supplement, pp. 256a. http://www.molbiolcell.org/. print. Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology Washington DC, USA December 08-12, 2001 ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 14 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Effect of **TP508**, a thrombin-related peptide, on Cbfa1, VEGF, and collagen type II expression during femoral fracture healing.
ACCESSION NUMBER: 2002:175479 BIOSIS
DOCUMENT NUMBER: PREV200200175479
TITLE: Effect of **TP508**, a thrombin-related peptide, on Cbfa1, VEGF, and collagen type II expression during femoral fracture healing.
AUTHOR(S): Wang, Hali (1); Convery, Jeremiah; Fowler, Christopher; Peters, Paul

CORPORATE SOURCE: (1) Research and Development, OrthoLogic, 1275 W. Washington St., Tempe, AZ, 58281 USA
SOURCE: Molecular Biology of the Cell, (Dec., 2000) Vol. 11, No. Supplement, pp. 243a. http://www.molbiolcell.org/. print. Meeting Info.: 40th American Society for Cell Biology Annual Meeting San Francisco, CA, USA December 09-13, 2000 ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 15 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Yeast two-hybrid analysis to identify receptor proteins that interact with thrombin or the thrombin peptide **TP508**.
ACCESSION NUMBER: 2002:165449 BIOSIS
DOCUMENT NUMBER: PREV200200165449
TITLE: Yeast two-hybrid analysis to identify receptor proteins that interact with thrombin or the thrombin peptide **TP508**.
AUTHOR(S): Saeed, Mohammad F. (1); Keherly, Michael J. (1); Nguyen, Yummy (1); Bergmann, John S. (1); Whitson, Brian S. (1); Carney, Darrell H. (1)
CORPORATE SOURCE: (1) Chrysalis BioTechnology, Inc., 2200 Market St., Suite 600, Galveston, TX, 77550 USA
SOURCE: Molecular Biology of the Cell, (Nov, 2001) Vol. 12, No. Supplement, pp. 330a. http://www.molbiolcell.org/. print. Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology Washington DC, USA December 08-12, 2001 ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 16 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Thrombin and thrombin peptide **TP508** (Chrysalin(R)) bind to a high affinity receptor that appears to be larger than known members of the proteolytically activated receptor (PAR) family.
ACCESSION NUMBER: 2002:165448 BIOSIS
DOCUMENT NUMBER: PREV200200165448
TITLE: Thrombin and thrombin peptide **TP508** (Chrysalin(R)) bind to a high affinity receptor that appears to be larger than known members of the proteolytically activated receptor (PAR) family.
AUTHOR(S): Bergmann, John S. (1); Laird, Aaron C.; Carney, Darrell H.
CORPORATE SOURCE: (1) Human Biological Chemistry and Genetics, University of Texas Medical Branch, 301 University Blvd., Galveston, TX, 77555 USA
SOURCE: Molecular Biology of the Cell, (Nov, 2001) Vol. 12, No. Supplement, pp. 330a. http://www.molbiolcell.org/. print. Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology Washington DC, USA December 08-12, 2001 ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 17 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Thrombin peptide **TP508** accelerates dermal wound healing with an immediate, delayed, or double treatment regimen: Role of leukocytes.
ACCESSION NUMBER: 2002:155690 BIOSIS
DOCUMENT NUMBER: PREV200200155690
TITLE: Thrombin peptide **TP508** accelerates dermal wound healing with an immediate, delayed, or double treatment regimen: Role of leukocytes.
AUTHOR(S): Norfleet, Andrea M. (1); Redin, William R.; Morshedi, Pasha J.; Carney, Darrell H.
CORPORATE SOURCE: (1) Chrysalis BioTechnology, 2200 Market Street, Suite 600,

Galveston, TX, 77550 USA
SOURCE: Molecular Biology of the Cell, (Dec., 2000) Vol. 11, No. Supplement, pp. 464a. http://www.molbiolcell.org/. print.
Meeting Info.: 40th American Society for Cell Biology Annual Meeting San Francisco, CA, USA December 09-13, 2000
ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 18 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI cDNA expression array analysis identifies early changes in fibroblast gene expression induced by thrombin peptide **TP508**.
ACCESSION NUMBER: 2002:155652 BIOSIS
DOCUMENT NUMBER: PREV200200155652
TITLE: cDNA expression array analysis identifies early changes in fibroblast gene expression induced by thrombin peptide **TP508**.
AUTHOR(S): Bergmann, John S. (1); Keherly, Michael J.; Carney, Darrell H.
CORPORATE SOURCE: (1) Human Biological Chemistry and Genetics, Univ Texas Medical Branch, 301 University Blvd., Galveston, TX, 77555 USA
SOURCE: Molecular Biology of the Cell, (Dec., 2000) Vol. 11, No. Supplement, pp. 456a-457a. http://www.molbiolcell.org/. print.
Meeting Info.: 40th American Society for Cell Biology Annual Meeting San Francisco, CA, USA December 09-13, 2000
ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 19 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Thrombin peptide **TP508** regulates BMP-2 and -7 expression by human osteoblasts.
ACCESSION NUMBER: 2001:562028 BIOSIS
DOCUMENT NUMBER: PREV200100562028
TITLE: Thrombin peptide **TP508** regulates BMP-2 and -7 expression by human osteoblasts.
AUTHOR(S): Bi, L. X. (1); Ji, Y. (1); Crowther, R. S. (1); Mainous, E. (1); Buford, W. L. (1)
CORPORATE SOURCE: (1) University of Texas Medical Branch, Galveston, TX USA
SOURCE: Journal of Bone and Mineral Research, (September, 2001) Vol. 16, No. Suppl. 1, pp. S261. print.
Meeting Info.: Twenty-Third Annual Meeting of the American Society for Bone and Mineral Research Phoenix, Arizona, USA October 12-16, 2001
ISSN: 0884-0431.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L10 ANSWER 20 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Effect of **TP508**, a synthetic thrombin peptide, on growth factor expression during femoral fracture healing.
ACCESSION NUMBER: 2001:561998 BIOSIS
DOCUMENT NUMBER: PREV200100561998
TITLE: Effect of **TP508**, a synthetic thrombin peptide, on growth factor expression during femoral fracture healing.
AUTHOR(S): Wang, H. (1); Convery, J. (1); Ryaby, J. T. (1)
CORPORATE SOURCE: (1) OrthoLogic, Tempe, AZ USA
SOURCE: Journal of Bone and Mineral Research, (September, 2001) Vol. 16, No. Suppl. 1, pp. S252. print.
Meeting Info.: Twenty-Third Annual Meeting of the American Society for Bone and Mineral Research Phoenix, Arizona, USA

October 12-16, 2001
ISSN: 0884-0431.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L10 ANSWER 21 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Thrombin peptide **TP508** accelerates closure of dermal excisions in animal tissue with surgically induced ischemia.
AB **TP508** is a synthetic peptide corresponding to amino acids 508 through 530 of human prothrombin. We previously demonstrated that a single topical application of **TP508** stimulates revascularization and healing of acute incisional and excisional wounds in normal, healthy rat skin. To determine if **TP508** would enhance wound healing in ischemic skin, we used bipedicle flaps, cranially based flaps, and free grafts to surgically create ischemic regions on the backs of rats. Full-thickness, circular excisions were made within the flaps or grafts and immediately treated with a single application of saline +- **TP508** (0.1 mug/wound). Compared to wound closure in normal skin, ischemic skin wounds exhibited delayed closure, and the length of delay correlated with the degree of surgically induced ischemia. **TP508** significantly accelerated closure in both normal and ischemic skin, resulting in closure rates that were increased within the first 7 days of wounding by 30% in normal tissue and bipedicle flaps, 50% in cranially based flaps, and 225% in free grafts. Moreover, in both flap models, **TP508** restored the rate of closure to a rate approximating the control rate observed in normal skin. Histological comparisons of wound tissue from normal skin and cranially based flaps showed that ischemia reduced early recruitment of inflammatory cells at day 1 but increased inflammatory cell numbers in wound beds at day 14. **TP508** treatment of ischemic flap wounds significantly increased early inflammatory cell recruitment and restored the normal rapid resolution of the inflammatory phase. In addition, at day 7, **TP508**-treated wounds appeared to have an increased number of large functional blood vessels compared to saline controls. These studies support the potential efficacy of **TP508** in treating ischemic wounds in humans.
ACCESSION NUMBER: 2001:170419 BIOSIS
DOCUMENT NUMBER: PREV200100170419
TITLE: Thrombin peptide **TP508** accelerates closure of dermal excisions in animal tissue with surgically induced ischemia.
AUTHOR(S): Norfleet, Andrea M.; Huang, Yuesheng; Sower, Laurie E.; Redin, William R.; Fritz, Richard R.; Carney, Darrell H. (1)
CORPORATE SOURCE: (1) Dept. of Human Biological Chemistry and Genetics, The University of Texas Medical Branch, 301 University Blvd., Galveston, TX, 77555-0645: dcarney@utmb.edu USA
SOURCE: Wound Repair and Regeneration, (November December, 2000) Vol. 8, No. 6, pp. 517-529. print.
ISSN: 1067-1927.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

L10 ANSWER 22 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Acceleration of full-thickness wound healing in normal rats by the synthetic thrombin peptide, **TP508**.
AB Thrombin is an essential factor in hemostasis, inflammation, and tissue repair. The synthetic thrombin peptide, **TP508**, binds to high-affinity thrombin receptors and mimics cellular effects of thrombin at sites of tissue injury. Treatment of full-thickness excisional wounds in normal rats with a single topical application of 0.1 mug **TP508** (14 pmol/cm2) reproducibly accelerates wound closure, yielding wounds that on average close 39% more than controls by day 7 ($p < 0.001$). Wounds

treated with 1.0 mug **TP508** are 35% and 43% ($p < 0.001$) smaller than controls on day 7 and 10, respectively. The early rate of closure is apprx40% greater in **TP508**-treated than vehicle-treated wounds (20 versus 14 mm2/day) and remains higher through day 7. Breaking strength after closure is slightly greater (15-23%) in wounds treated with **TP508** than with saline alone. Histologic comparisons show that **TP508** enhances recruitment of inflammatory cells to the wound site within 24 hours post-injury. **TP508** treatment also augments revascularization of injured tissue, as evidenced at day 7 by the larger size of functional vessels in the granulation tissue and by the directed development of blood vessels to wounds. These studies raise the possibility that **TP508** may be clinically useful in management of open wounds.

ACCESSION NUMBER: 2000:336305 BIOSIS
DOCUMENT NUMBER: PREV200000336305
TITLE: Acceleration of full-thickness wound healing in normal rats by the synthetic thrombin peptide, **TP508**.
AUTHOR(S): Stiernberg, Janet; Norfleet, Andrea M.; Redin, William R.; Warner, W. Scott; Fritz, Richard R.; Carney, Darrell H. (1)
CORPORATE SOURCE: (1) Department of Human Biological Chemistry and Genetics, University of Texas Medical Branch, 301 University Blvd., Galveston, TX, 77555-0645 USA
SOURCE: Wound Repair and Regeneration, (May June, 2000) Vol. 8, No. 3, pp. 204-215. print.
ISSN: 1067-1927.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

L10 ANSWER 23 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Effect of thrombin peptide, **TP508**, on proliferation and migration of human endothelial cells.
ACCESSION NUMBER: 2000:81715 BIOSIS
DOCUMENT NUMBER: PREV200000081715
TITLE: Effect of thrombin peptide, **TP508**, on proliferation and migration of human endothelial cells.
AUTHOR(S): Bergmann, John Scott (1); Meyers, Becky (1); Carney, Darrell H. (1)
CORPORATE SOURCE: (1) University of Texas Medical Branch, 301 University Blvd, Galveston, TX USA
SOURCE: Molecular Biology of the Cell, (Nov., 1999) Vol. 10, No. SUPPL., pp. 322a.
Meeting Info.: 39th Annual Meeting of the American Society for Cell Biology Washington, D.C., USA December 11-15, 1999 The American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 24 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Accelerated recruitment of inflammatory cells to dermal wounds by the thrombin peptide **TP508**.
ACCESSION NUMBER: 2000:63096 BIOSIS
DOCUMENT NUMBER: PREV200000063096
TITLE: Accelerated recruitment of inflammatory cells to dermal wounds by the thrombin peptide **TP508**.
AUTHOR(S): Norfleet, Andrea M. (1); Redin, William R. (1); Sower, Laurie E. (1); Stiernberg, Janet S. (1); Carney, Darrell H. (1)
CORPORATE SOURCE: (1) University of Texas Medical Branch, 301 University Blvd, Galveston, TX USA
SOURCE: Molecular Biology of the Cell, (Nov., 1999) Vol. 10, No. SUPPL., pp. 317a.
Meeting Info.: 39th Annual Meeting of the American Society

for Cell Biology Washington, D.C., USA December 11-15, 1999
The American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 25 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Thrombin peptide, **TP508**, induces proliferation and migration of keratinocytes.
ACCESSION NUMBER: 2000:62253 BIOSIS
DOCUMENT NUMBER: PREV200000062253
TITLE: Thrombin peptide, **TP508**, induces proliferation and migration of keratinocytes.
AUTHOR(S): Sower, Laurie E. (1); Huang, Yuesheng (1); Norfleet, Andrea (1); Carney, Darrell H. (1)
CORPORATE SOURCE: (1) The University of Texas Medical Branch, 11th and Mechanic, 504 Basic Science Bldg., Galveston, TX USA
SOURCE: Molecular Biology of the Cell, (Nov., 1999) Vol. 10, No. SUPPL., pp. 186a.
Meeting Info.: 39th Annual Meeting of the American Society for Cell Biology Washington, D.C., USA December 11-15, 1999
The American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 26 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Cell activation by thrombin peptide, **TP508**, stimulates a pattern of gene expression distinct from that induced by thrombin or SFLLRNP.
ACCESSION NUMBER: 2000:28711 BIOSIS
DOCUMENT NUMBER: PREV200000028711
TITLE: Cell activation by thrombin peptide, **TP508**, stimulates a pattern of gene expression distinct from that induced by thrombin or SFLLRNP.
AUTHOR(S): Fritz, Pam H. (1); Carney, Darrell H.
CORPORATE SOURCE: (1) University of Texas Medical Branch, 301 University Blvd., Galveston, TX, 77555-0645 USA
SOURCE: Molecular Biology of the Cell, (Nov., 1999) Vol. 10, No. SUPPL., pp. 50a.
Meeting Info.: 39th Annual Meeting of the American Society for Cell Biology Washington, D.C., USA December 11-15, 1999
The American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 27 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Thrombin peptide, **TP508**, inhibits collagenase production.
ACCESSION NUMBER: 1999:274103 BIOSIS
DOCUMENT NUMBER: PREV199900274103
TITLE: Thrombin peptide, **TP508**, inhibits collagenase production.
AUTHOR(S): Sower, L. E. (1); Arany, M. (1); Carney, D. H. (1)
CORPORATE SOURCE: (1) University of Texas Medical Branch, Galveston, TX, 77555-0645 USA
SOURCE: FASEB Journal, (March 15, 1999) Vol. 13, No. 5 PART 2, pp. A1146.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology 99 Washington, D.C., USA April 17-21, 1999 Federation of American Societies for Experimental Biology
. ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 28 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Thrombin peptide, **TP508**, induces differential gene expression in fibroblasts through a nonproteolytic activation pathway.
AB Prior studies have shown that synthetic peptides representing the domain of thrombin responsible for high-affinity binding to fibroblasts stimulate chemotactic and cell proliferative signals through a nonproteolytic mechanism. One of these peptides, **TP508**, has recently been shown to be chemotactic for neutrophils, to enhance collagen accumulation in wounds, to enhance revascularization of wounds, and to accelerate the healing of incisional and open wounds in normal animals and in animals with impaired healing. To determine whether **TP508** activates the proteolytically activated receptor for thrombin (PAR1), or the signals that are activated by PAR1, we treated human fibroblasts with **TP508** and the PAR1-activating peptide, SFLLRNP, and analyzed the effects of these peptides on gene expression using differential display reverse transcriptase polymerase chain reaction. **TP508** induces expression of a number of specific message fragments with short tyrosine kinase-like domains that are not induced by SFLLRNP. Sequencing full-length clones prepared by Marathon extension of **TP508** -induced fragments revealed that among the induced transcripts, there was a sequence with 88% homology to human annexin V. Northern analysis with authentic annexin V cDNA confirms that **TP508**, but not SFLLRNP, induces expression of annexin V in human fibroblasts. These results demonstrate that **TP508** activates a cellular response separate from that activated through PAR1 and supports the hypothesis that **TP508** acts through a separate nonproteolytically activated thrombin receptor that may be responsible for high-affinity thrombin binding and for nonproteolytic signals that are required for thrombin stimulation of cell proliferation.
ACCESSION NUMBER: 1999:175539 BIOSIS
DOCUMENT NUMBER: PREV199900175539
TITLE: Thrombin peptide, **TP508**, induces differential gene expression in fibroblasts through a nonproteolytic activation pathway.
AUTHOR(S): Sower, Laurie E.; Payne, Deborah A.; Meyers, Rebecca; Carney, Darrell H. (1)
CORPORATE SOURCE: (1) Department of Human Biological Chemistry and Genetics, University of Texas Medical Branch, 301 University Blvd., Galveston, TX, 77555-0645 USA
SOURCE: Experimental Cell Research, (March 15, 1999) Vol. 247, No. 2, pp. 422-431.
ISSN: 0014-4827.
DOCUMENT TYPE: Article
LANGUAGE: English

L10 ANSWER 29 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Thrombin peptide, **TP508**, enhances proliferation of peripheral blood mononuclear cells (PMBC) and T cells via a non-proteolytically activated receptor pathway.
ACCESSION NUMBER: 1999:25189 BIOSIS
DOCUMENT NUMBER: PREV199900025189
TITLE: Thrombin peptide, **TP508**, enhances proliferation of peripheral blood mononuclear cells (PMBC) and T cells via a non-proteolytically activated receptor pathway.
AUTHOR(S): Sower, L. E.; Klimpel, G. R.; Carney, D. H.
CORPORATE SOURCE: Dep. HBC and G, Univ. Texas Med. Branch, Houston, TX USA
SOURCE: Molecular Biology of the Cell, (Nov., 1998) Vol. 9, No. SUPPL., pp. 236A.
Meeting Info.: 38th Annual Meeting of the American Society for Cell Biology San Francisco, California, USA December 12-16, 1998 American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference

LANGUAGE: English

L10 ANSWER 30 OF 47 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Cellular antimicrobial action in wounds is stimulated by the thrombin peptide, **TP508**.
ACCESSION NUMBER: 1999:16004 BIOSIS
DOCUMENT NUMBER: PREV199900016004
TITLE: Cellular antimicrobial action in wounds is stimulated by the thrombin peptide, **TP508**.
AUTHOR(S): Stiernberg, J.; Sower, L. E.; Gerdes, L.; Ramakrishnan, S.; Redin, W. R.; Carney, D. H.
CORPORATE SOURCE: Dep. HBC and G, Univ. Texas Med. Branch, Houston, TX USA
SOURCE: Molecular Biology of the Cell, (Nov., 1998) Vol. 9, No. SUPPL., pp. 237A.
Meeting Info.: 38th Annual Meeting of the American Society for Cell Biology San Francisco, California, USA December 12-16, 1998 American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 31 OF 47 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor -
AN AAU78376 Peptide DGENE
AB The invention describes a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method involves administering an agonist to stimulate bone growth at a site in a subject (e.g. a farm animal, companion animal or laboratory animal), in need of osteoinduction, such as the site in need of a bone graft in a subject, a segmental bone gap, a bone void or a non-union fracture. This sequence represents a thrombin peptide derivative obtained from a serine esterase that can stimulate or activate the non-proteolytically activated thrombin receptor.
ACCESSION NUMBER: AAU78376 Peptide DGENE
TITLE: Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor -
INVENTOR: Carney D H; Crowther R S; Simmons D J; Yang J; Redin W R
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002005836 A2 20020124 27p
APPLICATION INFO: WO 2001-US22641 20010718
PRIORITY INFO: US 2000-219300P 20000719
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-303796 [34]
DESCRIPTION: Thrombin peptide derivative **TP508**.

L10 ANSWER 32 OF 47 DGENE (C) 2003 THOMSON DERWENT
TI Promoting cardiac tissue repair, stimulating revascularisation, stimulating vascular endothelial cell proliferation, and inhibiting vascular occlusion by using angiogenic thrombin derivative peptide -
AN AAM50858 Peptide DGENE
AB The present peptide comprises a thrombin-derived peptide, **TP508**, that includes a thrombin receptor binding domain sequence (see also AAM50856) and a serine esterase conserved sequence (see also AAM50857). The peptide is used in a claimed method for promoting cardiac tissue repair. It is administered during or following cardiac surgery by injection into cardiac tissue, and may be formulated as a sustained release formulation. The thrombin derivative peptide is also used in claimed methods of stimulating revascularisation, stimulating vascular endothelial cell proliferation, inhibiting vascular occlusion, and

inhibiting restenosis following balloon angioplasty, in which case it may be coated onto the catheter.

ACCESSION NUMBER: AAM50858 Peptide DGENE
TITLE: Promoting cardiac tissue repair, stimulating revascularisation, stimulating vascular endothelial cell proliferation, and inhibiting vascular occlusion by using angiogenic thrombin derivative peptide -
INVENTOR: Carney D H
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002004008 A2 20020117 24p
APPLICATION INFO: WO 2001-US21944 20010712
PRIORITY INFO: US 2000-217583P 20000712
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-179665 [23]
DESCRIPTION: Thrombin-derived peptide used to promote cardiac tissue repair.

L10 ANSWER 33 OF 47 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI PAR(1)-dependent and independent increases in COX-2 and PGE(2) in human colonic myofibroblasts stimulated by thrombin.
AB Sub epithelial myofibroblast-derived prostaglandin E(2) (PGE(2)) regulates epithelial chloride secretion in the intestine. Thrombin is elevated in inflammatory conditions of the bowel. Therefore, we sought to determine a role for thrombin in regulating PGE(2) synthesis by colonic myofibroblasts. Incubation of cultured CCD-18Co colonic myofibroblasts with thrombin, the proteinase-activated receptor 1 (PAR(1))-activating peptide (Cit-NH(2)), and peptides corresponding to 2 noncatalytic regions of thrombin (TP367 and **TP508**) for 18 h increased both cyclooxygenase (COX)-2 expression (immunocytochemistry) and PGE(2) synthesis (enzyme immunoassay). Inhibition of thrombin by D-Phe-Pro-Arg-chloromethylketone (PPACK) did not significantly reduce PGE(2) synthesis, which remained elevated compared with control. We also investigated the basic fibroblast growth factor (bFGF) dependence of thrombin-induced PGE(2) elevations. Recombinant human bFGF concentration dependently increased PGE(2) synthesis, and a bFGF neutralizing antibody inhibited PGE(2) synthesis induced by TP367 and **TP508** (-40%) and by thrombin (-20%) (but not Cit-NH(2)). Thrombin, therefore, upregulates COX-2-derived PGE(2) synthesis by both catalytic cleavage of PAR(1) and bFGF-dependent noncatalytic activity. This presents a novel mechanism by which intestinal myofibroblasts might regulate epithelial chloride secretion.

ACCESSION NUMBER: 2003163010 EMBASE
TITLE: PAR(1)-dependent and independent increases in COX-2 and PGE(2) in human colonic myofibroblasts stimulated by thrombin.
AUTHOR: Seymour M.L.; Zaidi N.F.; Hollenberg M.D.; MacNaughton W.K.
CORPORATE SOURCE: W.K. MacNaughton, Mucosal Inflammation Research Group, Univ. of Calgary, 3330 Hospital Drive NW, Calgary, Alta. T2N 4N1, Canada. wmacnaug@ucalgary.ca
SOURCE: American Journal of Physiology - Cell Physiology, (1 May 2003) 284/5 53-5 (C1185-C1192).
Refs: 42
ISSN: 0363-6143 CODEN: AJPCDD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
LANGUAGE: English
SUMMARY LANGUAGE: English

L10 ANSWER 34 OF 47 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Controlled release of an osteogenic peptide from injectable biodegradable polymeric composites.
AB Poly(D,L-lactic-co-glycolic acid)/poly(ethylene glycol) (PLGA/PEG) blend

microparticles loaded with the osteogenic peptide **TP508** were added to a mixture of poly(propylene fumarate) (PPF), poly(propylene fumarate)-diacrylate (PPF-DA), and sodium chloride (NaCl) for the fabrication of PPF composite scaffolds that could allow for tissue ingrowth as well as for the controlled release of **TP508** when implanted in an orthopedic defect site. In this study, PPF composites were fabricated and the in vitro release kinetics of **TP508** were determined. **TP508** loading within the PLGA/PEG microparticles, PEG content within the PLGA/PEG microparticles, the microparticle content of the PPF composite polymer component, and the leachable porogen initial mass percent of the PPF composites were varied according to a fractional factorial design and the effect of each variable on the release kinetics was determined for up to 28 days. Each composite formulation released **TP508** with a unique release profile. The initial release (release through day 1) of the PLGA/PEG microparticles was reduced upon inclusion in the PPF composite formulations. Day 1 normalized cumulative mass release from PPF composites ranged from 0.14.+-.0.01 to 0.41.+-.0.01, whereas the release from PLGA/PEG microparticles ranged from 0.31.+-.0.02 to 0.58.+-.0.01. After 28 days, PPF composites released 53.+-.4% to 86.+-.2% of the entrapped peptide resulting in cumulative mass releases ranging from 0.14.+-.0.01 .mu.g **TP508**/mm(3) scaffold to 2.46.+-.0.05 .mu.g **TP508**/mm(3) scaffold. The results presented here demonstrate that PPF composites can be used for the controlled release of **TP508** and that alterations in the composite's composition can lead to modulation of the **TP508** release kinetics. These composites can be used to explore the effects varied release kinetics and dosages on the formation of bone in vivo.

ACCESSION NUMBER: 2002446418 EMBASE
TITLE: Controlled release of an osteogenic peptide from injectable biodegradable polymeric composites.
AUTHOR: Hedberg E.L.; Tang A.; Crowther R.S.; Carney D.H.; Mikos A.G.
CORPORATE SOURCE: A.G. Mikos, Department of Bioengineering, Rice University, MS-142, P.O. Box 1892, Houston, TX 77251-1892, United States. mikos@rice.edu
SOURCE: Journal of Controlled Release, (5 Dec 2002) 84/3 (137-150). Refs: 39
ISSN: 0168-3659 CODEN: JCREEC
PUBLISHER IDENT.: S 0168-3659(02)00261-4
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

L10 ANSWER 35 OF 47 EMBASE
TI Thrombin peptide, **TP508**, stimulates angiogenic responses in animal models of dermal wound healing, in chick chorioallantoic membranes, and in cultured human aortic and microvascular endothelial cells.
AB The .alpha.-thrombin peptide, **TP508**, accelerates the healing of full-thickness wounds in both normal and ischemic skin. In wounds treated with **TP508**, a pattern of increased vascularization is consistently observed both grossly and microscopically when compared to wounds treated with saline. One possible mechanism by which the peptide accelerates wound healing is by promoting revascularization of granulation tissue at the injured site. To evaluate the angiogenic potential of **TP508**, the peptide was tested in the chick embryo chorioallantoic membrane (CAM), where it increased the density and size of CAM blood vessels relative to controls. Additionally, **TP508** stimulated chemokinesis and chemotaxis in a dose-dependent fashion in cultured human aortic and human microvascular endothelial cells. Taken together, these in vivo and in vitro data support an angiogenic role for **TP508** in

wound healing. A working model is presented to explain how this 23-amino-acid peptide, which lacks proteolytic activity, is generated during wound healing and contributes to the nonproteolytic functions associated with .alpha.-thrombin during tissue repair. .COPYRGT. 2002 Elsevier Science Inc. All rights reserved.

ACCESSION NUMBER: 2002098497 EMBASE
TITLE: Thrombin peptide, **TP508**, stimulates angiogenic responses in animal models of dermal wound healing, in chick chorioallantoic membranes, and in cultured human aortic and microvascular endothelial cells.
AUTHOR: Norfleet A.M.; Bergmann J.S.; Carney D.H.
CORPORATE SOURCE: D.H. Carney, Chrysalis BioTechnology, 2200 Market Street, Galveston, TX 77550, United States. dcarney@chrysalisbio.com
SOURCE: General Pharmacology: Vascular System, (2000) 35/5 (249-254).
Refs: 26
ISSN: 0306-3623 CODEN: GEPHDP
PUBLISHER IDENT.: S 0306-3623(01)00118-5
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 013 Dermatology and Venereology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L10 ANSWER 36 OF 47 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Thrombin peptide **TP508** accelerates closure of dermal excisions in animal tissue with surgically induced ischemia.
AB **TP508** is a synthetic peptide corresponding to amino acids 508 through 530 of human prothrombin. We previously demonstrated that a Single topical application of **TP508** stimulates revascularization and healing of acute incisional and excisional wounds in normal, healthy rat skin. To determine if **TP508** would enhance wound healing in ischemic skin, we used bipedicle flaps, cranially based flaps, and free grafts to surgically create ischemic regions on the backs of rats. Full-thickness, circular excisions were made within the flaps or grafts and immediately treated with a single application of saline .+-. **TP508** (0.1 .mu.g/wound). Compared to wound closure in normal skin, ischemic skin wounds exhibited delayed closure, and the length of delay correlated with the degree of surgically induced ischemia. **TP508** significantly accelerated closure in both normal and ischemic skin, resulting in closure rates that were increased within the first 7 days of wounding by 30% in normal tissue and bipedicle flaps, 50% in cranially based flaps, and 225% in free grafts. Moreover, in both flap models, **TP508** restored the rate of closure to a rate approximating the control rate observed in normal skin. Histological comparisons of wound tissue from normal skin and cranially based flaps showed that ischemia reduced early recruitment of inflammatory cells at day 1 but increased inflammatory cell numbers in wound beds at day 14. **TP508** treatment of ischemic flap wounds significantly increased early inflammatory cell recruitment and restored the normal rapid resolution of the inflammatory phase. In addition, at day 7, **TP508**-treated wounds appeared to have an increased number of large functional blood vessels compared to saline controls. These studies support the potential efficacy of **TP508** in treating ischemic wounds in humans.

ACCESSION NUMBER: 2001059952 EMBASE
TITLE: Thrombin peptide **TP508** accelerates closure of dermal excisions in animal tissue with surgically induced ischemia.
AUTHOR: Norfleet A.M.; Huang Y.; Sower L.E.; Redin W.R.; Fritz R.R.; Carney D.H.
CORPORATE SOURCE: Dr. D.H. Carney, Dept. of Human Biol. Chem./Genetics, Univ.

of Texas Medical Branch, 301 University Blvd., Galveston, TX 77555-0645, United States. dcarney@utmb.edu
SOURCE: Wound Repair and Regeneration, (2000) 8/6 (517-529). Refs: 33 ISSN: 1067-1927 CODEN: WREREU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L10 ANSWER 37 OF 47 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Acceleration of full-thickness wound healing in normal rats by the synthetic thrombin peptide, **TP508**.
AB Thrombin is an essential factor in hemostasis, inflammation, and tissue repair. The synthetic thrombin peptide, **TP508**, binds to high-affinity thrombin receptors and mimics cellular effects of thrombin at sites of tissue injury. Treatment of full-thickness excisional wounds in normal rats with a single topical application of 0.1 .mu.g **TP508** (14 pmol/cm2) reproducibly accelerates wound closure, yielding wounds that on average close 39% more than controls by day 7 ($p < 0.001$). Wounds treated with 1.0 .mu.g **TP508** are 35% and 43% ($p < 0.001$) smaller than controls on day 7 and 10, respectively. The early rate of closure is .apprx.40% greater in **TP508**-treated than vehicle-treated wounds (20 versus 14 mm2/day) and remains higher through day 7. Breaking strength after closure is slightly greater (15-23%) in wounds treated with **TP508** than with saline alone. Histologic comparisons show that **TP508** enhances recruitment of inflammatory cells to the wound site within 24 hours post- injury. **TP508** treatment also augments revascularization of injured tissue, as evidenced at day 7 by the larger size of functional vessels in the granulation tissue and by the directed development of blood vessels to wounds. These studies raise the possibility that **TP508** may be clinically useful in management of open wounds.
ACCESSION NUMBER: 2000228994 EMBASE
TITLE: Acceleration of full-thickness wound healing in normal rats by the synthetic thrombin peptide, **TP508**.
AUTHOR: Stiernberg J.; Norfleet A.M.; Redin W.R.; Warner W.S.; Fritz R.R.; Carney D.H.
CORPORATE SOURCE: Dr. D.H. Carney, Dept. of Human Biol. Chem./Genetics, University of Texas Medical Branch, 301 University Blvd., Galveston, TX 77555-0645, United States. dcarney@utmb.edu
SOURCE: Wound Repair and Regeneration, (2000) 8/3 (204-215). Refs: 41 ISSN: 1067-1927 CODEN: WREREU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
013 Dermatology and Venereology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L10 ANSWER 38 OF 47 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Thrombin peptide, **TP508**, induces differential gene expression in fibroblasts through a nonproteolytic activation pathway.
AB Prior studies have shown that synthetic peptides representing the domain of thrombin responsible for high-affinity binding to fibroblasts stimulate chemotactic and cell proliferative signals through a nonproteolytic mechanism. One of these peptides, **TP508**, has recently been shown to be chemotactic for neutrophils, to enhance collagen accumulation in wounds, to enhance revascularization of wounds, and to accelerate the healing of incisional and open wounds in normal animals and in animals

with impaired healing. To determine whether **TP508** activates the proteolytically activated receptor for thrombin (PAR1), or the signals that are activated by PAR1, we treated human fibroblasts with **TP508** and the PAR1-activating peptide, SFLLRNP, and analyzed the effects of these peptides on gene expression using differential display reverse transcriptase polymerase chain reaction. **TP508** induces expression of a number of specific message fragments with short tyrosine kinase-like domains that are not induced by SFLLRNP. Sequencing fulllength clones prepared by Marathon extension of **TP508**-induced fragments revealed that among the induced transcripts, there was a sequence with 88% homology to human annexin V. Northern analysis with authentic annexin V cDNA confirms that **TP508**, but not SFLLRNP, induces expression of annexin V in human fibroblasts. These results demonstrate that **TP508** activates a cellular response separate from that activated through PAR1 and supports the hypothesis that **TP508** acts through a separate nonproteolytically activated thrombin receptor that may be responsible for high-affinity thrombin binding and for nonproteolytic signals that are required for thrombin stimulation of cell proliferation.

ACCESSION NUMBER: 1999293806 EMBASE
TITLE: Thrombin peptide, **TP508**, induces differential gene expression in fibroblasts through a nonproteolytic activation pathway.
AUTHOR: Sower L.E.; Payne D.A.; Meyers R.; Carney D.H.
CORPORATE SOURCE: D.H. Carney, Dept. of Human Biological Chem./Gen., University of Texas Medical Branch, 301 University Blvd., Galveston, TX 77555-0645, United States. dcarney@marlin.utmb.edu
SOURCE: Experimental Cell Research, (15 Mar 1999) 247/2 (422-431). Refs: 83
ISSN: 0014-4827 CODEN: ECREAL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

L10 ANSWER 39 OF 47 WPIDS (C) 2003 THOMSON DERWENT
TI Promoting healing of chronic dermal skin ulcer such as diabetic ulcer, on a subject, by contacting the skin ulcer with an agonist of non-proteolytically activated thrombin receptor.
AN 2003-289898 [28] WPIDS
AB WO2003013569 A UPAB: 20030501
NOVELTY - Promoting (M) healing of a chronic dermal skin ulcer on a subject, comprises contacting the chronic dermal skin ulcer with a thrombin peptide derivative.

DETAILED DESCRIPTION - Promoting (M) healing of a chronic dermal skin ulcer on a subject comprises contacting the chronic dermal skin ulcer with a thrombin peptide derivative having the amino acid sequence (S1):

R1-Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-R2 (S1)

R1-Asp-Asn-Met-Phe-Cys-Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-Met-Lys-Ser-Pro-Phe-R2 (S2)

R1 = -H or R3-C(O)-;
R2 = -OH or -NR4R5;
R3 = -H or 1-6C alkyl group; and
R4 and R5 = -H, 1-6C alkyl group or taken together with nitrogen atom to which they are bonded, a non-aromatic heterocyclic group, provided that zero, one, two or three amino acids at positions 1-9 and 14-23 in the thrombin peptide derivative differ from the amino acid at the corresponding position of (S1), or positions 1-14 and 19-33 of the thrombin peptide derivative differ from the amino acid at the corresponding position of (S2), an N-terminal truncated fragment of the thrombin peptide derivative having at least 14 amino acids or a C-terminal

truncated fragment of the thrombin peptide derivative having at least 18 amino acids.

ACTIVITY - Antiulcer.

A multi-center, randomized, double blind, three-arm Phase IIa pilot study evaluating synthetic thrombin peptide **TP508** for accelerating the healing of chronic diabetic ulcers was designed. Patients were randomized to one of three topical treatment groups: 1 micro g of **TP508** in saline applied twice weekly, 10 micro g of **TP508** in saline applied twice weekly, or saline placebo applied twice weekly. All patients received a regiment of standard diabetic ulcer care consisting of initial sharp debridement, wound cleansing, wound dressing and wound pressure off loading. Wounds were evaluated twice a week for 20 weeks or until wound closure. Blood chemistry and hematology tests were performed at patient enrollment, and at weeks 5, 10, 15 and 20. A radiographic assessment was conducted every 5 weeks to study effects on underlying bone composition. The primary efficacy endpoint was the proportion of patients that achieve full wound closure. Full wound closure was defined as 100% epithelialization, with no drainage and no infection, as determined by visual inspection by the clinician. Three different patient analysis groups were defined to better study the efficacy endpoints. The intent-to-treat (ITT) group included all 60 patients receiving study drug and was primarily used for safety evaluation. The per-protocol (PP) group included 40 patients that met a predefined set of criteria meant to assure the highest compliance with the protocol. The efficacy group included 46 patients which met standards that were chosen prior to unblinding to be most relevant to allow an accurate evaluation of wound healing. Primary endpoint results were described for each patient group. The primary efficacy endpoint results showed a dose response relationship for 100% closure in all populations examined, with 1 micro g treatments resulting in 4-15% more closure than saline placebo controls, and 10 micro g treatments resulting in 13-24% more closure than saline placebo controls. Specifically, in the PP treatment group, 5 of 15 or 33% healed in the saline placebo group, 5 of 11 or 45% healed in 1 micro g treatment group, and 8 of 14 or 57% healed in the 10 micro g group. In the efficacy (EF) group selected to include wounds slightly smaller and slightly larger than those in the stricter per protocol group, this trend was again seen with 38% healing in the placebo group, 53% healing in the 1 mu g group, and 60% healing in the 10 micro g group. The difference was again noted in the ITT population, although the percentage that healed in the saline placebo group was larger (48%) because this group included several small and superficial wounds that healed, but did not meet protocol to be defined as chronic diabetic wounds for the study. These results compared favorably to clinical trials for Regranex (RTM), where data compiled from 4 controlled randomized clinical trials showed that 83 of 254 or 33% of the vehicle placebo wounds healed by 20 weeks and 122 of 285 or 43% of the Regranex (RTM)-treated wounds healed by 20 weeks. These results showed an increased percentage of ulcer closure for patients treated with **TP508** and indicated median healing times that reflected a faster rate of healing.

MECHANISM OF ACTION - Agonist of non-proteolytically activated thrombin receptor.

USE - (M) is useful for promoting healing of a chronic dermal skin ulcer, especially diabetic ulcer, decubitus ulcer, venous stasis ulcer or arterial ulcer, on a companion animal, farm animal or laboratory animal (claimed).

Dwg.0/0

ACCESSION NUMBER: 2003-289898 [28] WPIDS
DOC. NO. CPI: C2003-075228
TITLE: Promoting healing of chronic dermal skin ulcer such as diabetic ulcer, on a subject, by contacting the skin ulcer with an agonist of non-proteolytically activated thrombin receptor.
DERWENT CLASS: B04 B05
INVENTOR(S): CARNEY, D H

PATENT ASSIGNEE(S): (TEXA) UNIV TEXAS SYSTEM
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003013569	A2	20030220	(200328)*	EN	19

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003013569	A2	WO 2002-US1151	20020116

PRIORITY APPLN. INFO: US 2001-308198P 20010727

L10 ANSWER 40 OF 47 WPIDS (C) 2003 THOMSON DERWENT
TI Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor.
AN 2002-303796 [34] WPIDS
AB WO 200205836 A UPAB: 20020528
NOVELTY - Stimulating (M) bone growth at a site in a subject in need of osteoinduction, involves administering to the site, an agonist (I) of the non-proteolytically activated thrombin receptor.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a pharmaceutical composition (PC) comprising an implantable, biocompatible carrier and (I).

ACTIVITY - Osteopathic.

MECHANISM OF ACTION - Stimulator of bone growth; agonist of activated thrombin receptor

12.5 cm segmental defect was created in each ulna of 20 male New Zealand rabbits. The bilateral ulnar osteotomies were created exactly the same size by using a small metal guide to direct the cutting blade of the oscillating microsaw. Each rabbit acted as its own control, thus the left defect was filled with microspheres not containing **TP508**, while the right defect was filled with microspheres containing 100 or 200 micro g **Tp508** (10 animals/group). Rabbits given bilateral ulnar osteomies were randomly divided into two groups. The first group received 100 micro g of **TP508** in microspheres (30 mg) in the right limb and microspheres alone in the left limb. The second group was treated similarly, but received 200 mu g of **TP508**. Animals were X-rayed at 2-week intervals, beginning at week 3, and sacrificed at 9 weeks. 100 micro g of **TP508** stimulated mineralization in the defect at 3 and 5 weeks post-surgery. X-rays at 7 and 9 weeks appeared similar to those obtained at 5 weeks. Animals were sacrificed at 9 weeks post-surgery and the ulna-radius was removed and photographed. In most cases a large defect was visible in ulnas from the control limbs, in contrast with the **TP508**-treated limbs, in which most of the defects were successfully closed. After sacrifice at 9 weeks post-surgery, repair strength was measured by torsion testing. The results showed that at 100 micro g, **TP508** more than doubled the mechanical strength of the healing defect as measured by all the parameters tested. Even stronger repairs were noted in the 200 micro g group, with most parameters being approximately 50% higher than those seen in the low dose treatment group.

USE - (M) is useful for stimulating bone growth at a site in a

subject (e.g. a farm animal, companion animal or laboratory animal), in need of osteoinduction, such as the site in need of a bone graft in a subject, a segmental bone gap, a bone void or a non-union fracture (claimed).
Dwg.0/0

ACCESSION NUMBER: 2002-303796 [34] WPIDS
DOC. NO. CPI: C2002-088279
TITLE: Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor.
DERWENT CLASS: A96 B04
INVENTOR(S): CARNEY, D H; CROWTHER, R S; REDIN, W R; SIMMONS, D J; YANG, J
PATENT ASSIGNEE(S): (TEXA) UNIV TEXAS SYSTEM
COUNTRY COUNT: 97
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002005836	A2	20020124	(200234)*	EN	27
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001076977	A	20020130	(200236)		
US 2002128202	A1	20020912	(200262)		
US 2002182205	A1	20021205	(200301)		
EP 1301196	A2	20030416	(200328)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2002005836	A2		WO 2001-US22641	20010718
AU 2001076977	A		AU 2001-76977	20010718
US 2002128202	A1	Provisional	US 2000-219300P	20000719
			US 2001-909122	20010719
US 2002182205	A1	Provisional	US 2000-219300P	20000719
		Cont of	US 2001-909122	20010719
			US 2002-50692	20020116
EP 1301196	A2		EP 2001-954752	20010718
			WO 2001-US22641	20010718

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001076977	A	Based on	WO 200205836
EP 1301196	A2	Based on	WO 200205836

PRIORITY APPLN. INFO: US 2000-219300P 20000719; US 2001-909122 20010719; US 2002-50692 20020116

L10 ANSWER 41 OF 47 WPIDS (C) 2003 THOMSON DERWENT
TI Promoting cardiac tissue repair, stimulating revascularization, stimulating vascular endothelial cell proliferation, and inhibiting vascular occlusion by using angiogenic thrombin derivative peptide.
AN 2002-179665 [23] WPIDS
AB WO 200204008 A UPAB: 20020411

NOVELTY - Promoting cardiac tissue repair or stimulating revascularization, stimulating vascular endothelial cell proliferation, inhibiting restenosis in a patient following balloon angioplasty, and for inhibiting vascular occlusion in a patient by administering an angiogenic thrombin derivative peptide (I) to cardiac tissue or blood vessels.

ACTIVITY - Vasotropic; cardiant.

(I) was tested for vasotropic and cardiant activity. Yucatan minipigs had toroid shaped ameroid occluders placed on their proximal left circumflex arteries. The ameroid imbibed water over time, causing constriction of the vessel. Occlusion was verified four weeks after surgery by contrast enhanced angiography. At that time, each animal's chest was reopened, where upon the region of ischemia was injected with a slow release formulation of **TP508** (100 micro l, i.e., **TP508**-containing poly(D,L-lactide-co-glycolide) (PLGA) microspheres, suspended in a Pluronic gel, into 10 sites (100 micro l/site) in the ischemic area. Controls received PLGA microspheres in Pluronic gel without **TP508**. Baseline, and post-treatment angiograms and echocardiograms were obtained. Indices for myocardial wall thickening and cardiac ejection fraction showed trends that **TP508** treated animals tolerated dobutamine-induced stress better than controls. After 3 weeks, the animals were evaluated with contrast enhanced echocardiography. Initial results on this limited number of animals demonstrated that **TP508** treated animals under dobutamine stress had a slightly larger increase in ejection fraction and better maintained wall thickening compared to controls. Thus, this treatment appears to help restore functionality to the ischemic heart muscle.

MECHANISM OF ACTION - Angiogenic proliferation and endothelial cells migration inducer.

USE - The method utilizing (I) is useful for promoting cardiac tissue repair, stimulating revascularization, stimulating vascular endothelial cell proliferation, inhibiting restenosis in a patient following balloon angioplasty, and for inhibiting vascular occlusion in a patient (claimed).

Dwg.0/3

ACCESSION NUMBER: 2002-179665 [23] WPIDS
DOC. NO. CPI: C2002-055805
TITLE: Promoting cardiac tissue repair, stimulating revascularization, stimulating vascular endothelial cell proliferation, and inhibiting vascular occlusion by using angiogenic thrombin derivative peptide.
DERWENT CLASS: B04 B07 D22
INVENTOR(S): CARNEY, D H
PATENT ASSIGNEE(S): (TEXA) UNIV TEXAS SYSTEM
COUNTRY COUNT: 97
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002004008	A2	20020117	(200223)*	EN	24
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001078907	A	20020121	(200234)		
US 2002061852	A1	20020523	(200239)		
EP 1253937	A2	20021106	(200281)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 2002187933	A1	20021212	(200301)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

WO 2002004008 A2		WO 2001-US21944 20010712
AU 2001078907 A		AU 2001-78907 20010712
US 2002061852 A1	Provisional	US 2000-217583P 20000712
		US 2001-904090 20010712
EP 1253937 A2		EP 2001-957136 20010712
		WO 2001-US21944 20010712
US 2002187933 A1	Provisional	US 2000-217583P 20000712
	Cont of	US 2001-904090 20010712
		US 2002-50611 20020116

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001078907	A	Based on	WO 200204008
EP 1253937	A2	Based on	WO 200204008

PRIORITY APPLN. INFO: US 2000-217583P 20000712; US 2001-904090 20010712; US 2002-50611 20020116

L10 ANSWER 42 OF 47 USPATFULL

TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor

AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an NPAR agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:344424 USPATFULL
TITLE:	Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S):	Carney, Darrell H., Dickinson, TX, UNITED STATES Crowther, Roger S., League City, TX, UNITED STATES Stiernberg, Janet, Paris, TX, UNITED STATES Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S):	Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002198154	A1	20021226
APPLICATION INFO.:	US 2002-50688	A1	20020116 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-909348, filed on 19 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS:	28
EXEMPLARY CLAIM:	1
LINE COUNT:	862

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 43 OF 47 USPATFULL
TI Methods of therapy with thrombin derived peptides
AB The present invention relates to a method for promoting cardiac tissue repair comprising administering to the cardiac tissue a therapeutically effective amount of an angiogenic thrombin derivative peptide and/or inhibiting or reducing vascular occlusion or restenosis. The invention also relates to methods of stimulating revascularization. In yet another embodiment, the invention relates to the use of thrombin derivative peptides in the manufacture of a medicament for the methods described herein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:330250 USPATFULL		
TITLE:	Methods of therapy with thrombin derived peptides		
INVENTOR(S):	Carney, Darrell H., Dickinson, TX, UNITED STATES		
PATENT ASSIGNEE(S):	Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002187933	A1	20021212
APPLICATION INFO.:	US 2002-50611	A1	20020116 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2001-904090, filed on 12 Jul 2001, PENDING		
	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-217583P	20000712 (60)	
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133		
NUMBER OF CLAIMS:	28		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	2 Drawing Page(s)		
LINE COUNT:	716		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 44 OF 47 USPATFULL
TI Stimulation of bone growth with thrombin peptide derivatives
AB Disclosed is a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:322044 USPATFULL		
TITLE:	Stimulation of bone growth with thrombin peptide derivatives		
INVENTOR(S):	Carney, Darrell H., Dickinson, TX, UNITED STATES Crowther, Roger S., League City, TX, UNITED STATES Simmons, David J., St. Louis, MO, UNITED STATES Yang, Jinping, Galveston, TX, UNITED STATES Redin, William R., Dickinson, TX, UNITED STATES		
PATENT ASSIGNEE(S):	Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002182205	A1	20021205
APPLICATION INFO.:	US 2002-50692	A1	20020116 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2001-909122, filed on 19 Jul 2001, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219300P	20000719 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS: 46
EXEMPLARY CLAIM: 1
LINE COUNT: 846
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 45 OF 47 USPATFULL
TI Stimulation of bone growth with thrombin peptide derivatives
AB Disclosed is a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:236005 USPATFULL
TITLE: Stimulation of bone growth with thrombin peptide derivatives
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Simmons, David J., St. Louis, MO, UNITED STATES
Yang, Jinping, Galveston, TX, UNITED STATES
Redin, William R., Dickinson, TX, UNITED STATES
PATENT ASSIGNEE(S): The Board of Regents, The University of TX. System (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002128202	A1	20020912
APPLICATION INFO.:	US 2001-909122	A1	20010719 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219300P	20000719 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1
LINE COUNT: 797
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 46 OF 47 USPATFULL
TI Methods of therapy with thrombin derived peptides
AB The present invention relates to a method for promoting cardiac tissue repair comprising administering to the cardiac tissue a therapeutically effective amount of an angiogenic thrombin derivative peptide and/or inhibiting or reducing vascular occlusion or restenosis. The invention also relates to methods of stimulating revascularization. In yet another embodiment, the invention relates to the use of thrombin derivative peptides in the manufacture of a medicament for the methods described herein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:119864 USPATFULL
TITLE: Methods of therapy with thrombin derived peptides
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES

PATENT ASSIGNEE(S): The Board of Regents, The University of Texas System (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002061852	A1	20020523
APPLICATION INFO.:	US 2001-904090	A1	20010712 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-217583P	20000712 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 683
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 47 OF 47 USPATFULL
TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an NPAR agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:78716 USPATFULL
TITLE: Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S): The Board of Regents, The University of Texas System (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002042373	A1	20020411
APPLICATION INFO.:	US 2001-909348	A1	20010719 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 836
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
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NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 13	Nov 18	DKILIT has been renamed APOLLIT
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NEWS 15	Dec 04	CSA files on STN
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NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
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NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 20	EVENTLINE will be removed from STN
NEWS 28	Mar 24	PATDPAFULL now available on STN
NEWS 29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 30	Apr 11	Display formats in DGENE enhanced
NEWS 31	Apr 14	MEDLINE Reload
NEWS 32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 33	Apr 21	Indexing from 1947 to 1956 being added to records in CA/CAPLUS
NEWS 34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 35	Apr 28	RDISCLOSURE now available on STN
NEWS 36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 39	May 16	CHEMREACT will be removed from STN
NEWS 40	May 19	Simultaneous left and right truncation added to WSCA
NEWS 41	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation

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 NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
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=> s NPAR or non-proteolytic thrombin receptor
L1          93 NPAR OR NON-PROTEOLYTIC THROMBIN RECEPTOR

=> s TP508
L2          55 TP508
```

=> s l1 and agonist
L3 11 L1 AND AGONIST

=> d l3 ti abs ibib tot

bad date

L3 ANSWER 1 OF 11 MEDLINE
TI Green tea epigallocatechin-3-gallate inhibits platelet signalling pathways triggered by both proteolytic and non-proteolytic agonists.
AB Epigallocatechin-3-gallate (EGCG), a component of green tea, inhibits human platelet aggregation and cytosolic [Ca(2+)](c) increases more strongly when these processes are induced by thrombin than by the **non-proteolytic thrombin receptor** activating peptide (TRAP), thromboxane mimetic U46619, or fluoroaluminate. In line with the previously demonstrated EGCG anti-proteolytic activity, a marked inhibition on aggregation is obtained by pre-incubation of thrombin with EGCG prior to addition to cellular suspension. The catechin also reduces cellular Ca(2+) influx following thapsigargin-induced calcium emptying of endoplasmic reticulum, and the **agonist**-promoted cellular protein tyrosine phosphorylation. Both tyrosine kinases Syk and Lyn, immuno-precipitated from stimulated platelets, are greatly inhibited upon cellular pre-incubation with EGCG, which also inhibits the in vitro auto-phosphorylation and exogenous activity of these two enzymes purified from rat spleen. Both thrombin-induced aggregation and [Ca(2+)](c) increase are reduced in platelets from rats that drank green tea solutions. It is concluded that EGCG inhibits platelet activation, by hindering the thrombin proteolytic activity, and by reducing the **agonist**-induced [Ca(2+)](c) increase through inhibition of Syk and Lyn activities.
ACCESSION NUMBER: 2003200249 IN-PROCESS
DOCUMENT NUMBER: 22605855 PubMed ID: 12719785
TITLE: Green tea epigallocatechin-3-gallate inhibits platelet signalling pathways triggered by both proteolytic and non-proteolytic agonists.
AUTHOR: Deana Renzo; Turetta Loris; Donella-Deana Arianna; Dona Massimo; Maria Brunati Anna; De Michiel Lucia; Garbisa Spiridione
CORPORATE SOURCE: Department of Biological Chemistry and Institute of the Neuroscience of the Italian National Research Council (CNR), University of Padova, Italy, E-mail:. arianna.donella@unipd.it
SOURCE: THROMBOSIS AND HAEMOSTASIS, (2003 May) 89 (5) 866-74. Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030430
Last Updated on STN: 20030430

L3 ANSWER 2 OF 11 USPATFULL
TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an **agonist** of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an **NPAR agonist**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:344424 USPATFULL
TITLE: Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S): Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002198154	A1	20021226
APPLICATION INFO.:	US 2002-50688	A1	20020116 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-909348, filed on 19 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
LINE COUNT: 862
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 3 OF 11 USPATFULL
TI Stimulation of bone growth with thrombin peptide derivatives
AB Disclosed is a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method comprises the step of administering a therapeutically effective amount of an **agonist** of the non-proteolytically activated thrombin receptor to the site.

App'l.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:322044 USPATFULL
TITLE: Stimulation of bone growth with thrombin peptide derivatives
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Simmons, David J., St. Louis, MO, UNITED STATES
Yang, Jinping, Galveston, TX, UNITED STATES
Redin, William R., Dickinson, TX, UNITED STATES
PATENT ASSIGNEE(S): Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002182205	A1	20021205
APPLICATION INFO.:	US 2002-50692	A1	20020116 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-909122, filed on 19 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219300P	20000719 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS: 46

EXEMPLARY CLAIM: 1
LINE COUNT: 846
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 4 OF 11 USPATFULL
TI Stimulation of bone growth with thrombin peptide derivatives
AB Disclosed is a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method comprises the step of administering a therapeutically effective amount of an **agonist** of the non-proteolytically activated thrombin receptor to the site.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:236005 USPATFULL
TITLE: Stimulation of bone growth with thrombin peptide derivatives
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Simmons, David J., St. Louis, MO, UNITED STATES
Yang, Jinping, Galveston, TX, UNITED STATES
Redin, William R., Dickinson, TX, UNITED STATES
PATENT ASSIGNEE(S): The Board of Regents, The University of TX. System (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002128202	A1	20020912
APPLICATION INFO.:	US 2001-909122	A1	20010719 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219300P	20000719 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1
LINE COUNT: 797
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 5 OF 11 USPATFULL
TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an **agonist** of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an **NPAR agonist**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:78716 USPATFULL
TITLE: Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S): The Board of Regents, The University of Texas System (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002042373	A1	20020411
APPLICATION INFO.:	US 2001-909348	A1	20010719 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 836
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 6 OF 11 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an **agonist** of non-proteolytically activated thrombin receptor -
AN AAE20159 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an **agonist** of non-proteolytically activated thrombin receptor (**NPAR**). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of **NPAR agonist** to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is human thrombin peptide derivative which serves as a **NPAR agonist**.
ACCESSION NUMBER: AAE20159 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an **agonist** of non-proteolytically activated thrombin receptor -
INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Human thrombin peptide derivative #2.

Considered

L3 ANSWER 7 OF 11 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an **agonist** of non-proteolytically activated thrombin receptor -
AN AAE20158 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an **agonist** of non-proteolytically activated thrombin receptor (**NPAR**). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of **NPAR agonist** to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is human thrombin peptide derivative which serves as a **NPAR agonist**.
ACCESSION NUMBER: AAE20158 peptide DGENE

TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an **agonist** of non-proteolytically activated thrombin receptor -
INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Human thrombin peptide derivative #1.

L3 ANSWER 8 OF 11 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an **agonist** of non-proteolytically activated thrombin receptor -
AN AAE20157 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an **agonist** of non-proteolytically activated thrombin receptor (**NPAR**). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of **NPAR agonist** to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is human thrombin peptide. The derivatives of thrombin peptide which serves as a **NPAR agonist**.
ACCESSION NUMBER: AAE20157 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an **agonist** of non-proteolytically activated thrombin receptor -
INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Human thrombin peptide.

L3 ANSWER 9 OF 11 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an **agonist** of non-proteolytically activated thrombin receptor -
AN AAE20156 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an **agonist** of non-proteolytically activated thrombin receptor (**NPAR**). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of **NPAR agonist** to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is serine esterase conserved peptide. This sequence is present in the thrombin peptide derivatives which serve as a **NPAR agonist**.
ACCESSION NUMBER: AAE20156 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an **agonist** of non-proteolytically activated thrombin receptor -

INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Serine esterase conserved peptide #2.

L3 ANSWER 10 OF 11 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an **agonist** of non-proteolytically activated thrombin receptor -
AN AAE20155 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an **agonist** of non-proteolytically activated thrombin receptor (**NPAR**). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of **NPAR agonist** to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is serine esterase conserved peptide. This sequence is present in the thrombin peptide derivatives which serve as a **NPAR agonist**.
ACCESSION NUMBER: AAE20155 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an **agonist** of non-proteolytically activated thrombin receptor -
INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Serine esterase conserved peptide #1.

L3 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2003 ACS
TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amt. of an **agonist** of the non-proteolytically activated thrombin receptor (**NPAR**) to the site. Also disclosed is a method of stimulating the proliferation and expansion of chondrocytes in vitro. The method comprises culturing chondrocytes in the presence of a stimulating amt. of an **NPAR agonist**. The **NPAR agonist** TP508 (a thrombin peptide deriv.) stimulated cartilage growth in rabbits.
ACCESSION NUMBER: 2002:89846 HCAPLUS
DOCUMENT NUMBER: 136:145245
TITLE: Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H.; Crowther, Roger S.; Stiernberg, Janet; Bergmann, John
PATENT ASSIGNEE(S): The Board of Regents, the University of Texas System, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002007748	A2	20020131	WO 2001-US22668	20010719
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002042373	A1	20020411	US 2001-909348	20010719
EP 1259598	A2	20021127	EP 2001-952846	20010719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002198154	A1	20021226	US 2002-50688	20020116

PRIORITY APPLN. INFO.: US 2000-219800P P 20000720
US 2001-909348 A1 20010719
WO 2001-US22668 W 20010719
OTHER SOURCE(S): MARPAT 136:145245

=> d his

(FILE 'HOME' ENTERED AT 16:00:18 ON 27 MAY 2003)

FILE 'MEDLINE, USPATFULL, DGENE, EMBASE, FSTA, WPIDS, JICST-EPLUS, BIOBUSINESS, BIOSIS, HCAPLUS' ENTERED AT 16:01:01 ON 27 MAY 2003
L1 93 S NPAR OR NON-PROTEOLYTIC THROMBIN RECEPTOR
L2 55 S TP508
L3 11 S L1 AND AGONIST

=> s l1 and l2
L4 7 L1 AND L2

=> d l4 ti abs ibib tot

L4 ANSWER 1 OF 7 USPATFULL
TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an **NPAR** agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:344424 USPATFULL
TITLE: Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES

PATENT ASSIGNEE(S): Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002198154	A1	20021226
APPLICATION INFO.:	US 2002-50688	A1	20020116 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-909348, filed on 19 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
LINE COUNT: 862
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 2 OF 7 USPATFULL
TI Stimulation of bone growth with thrombin peptide derivatives
AB Disclosed is a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:322044 USPATFULL
TITLE: Stimulation of bone growth with thrombin peptide derivatives
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Simmons, David J., St. Louis, MO, UNITED STATES
Yang, Jinping, Galveston, TX, UNITED STATES
Redin, William R., Dickinson, TX, UNITED STATES
PATENT ASSIGNEE(S): Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002182205	A1	20021205
APPLICATION INFO.:	US 2002-50692	A1	20020116 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-909122, filed on 19 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219300P	20000719 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS: 46
EXEMPLARY CLAIM: 1
LINE COUNT: 846
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 3 OF 7 USPATFULL
TI Stimulation of bone growth with thrombin peptide derivatives
AB Disclosed is a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method comprises the step of

administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:236005 USPATFULL
TITLE:	Stimulation of bone growth with thrombin peptide derivatives
INVENTOR(S):	Carney, Darrell H., Dickinson, TX, UNITED STATES Crowther, Roger S., League City, TX, UNITED STATES Simmons, David J., St. Louis, MO, UNITED STATES Yang, Jinping, Galveston, TX, UNITED STATES Redin, William R., Dickinson, TX, UNITED STATES
PATENT ASSIGNEE(S):	The Board of Regents, The University of TX. System (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002128202	A1	20020912	
APPLICATION INFO.:	US 2001-909122	A1	20010719	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-219300P	20000719	(60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS:	37
EXEMPLARY CLAIM:	1
LINE COUNT:	797

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 4 OF 7 USPATFULL

TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor

AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an **NPAR** agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:78716 USPATFULL
TITLE:	Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S):	Carney, Darrell H., Dickinson, TX, UNITED STATES Crowther, Roger S., League City, TX, UNITED STATES Stiernberg, Janet, Paris, TX, UNITED STATES Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S):	The Board of Regents, The University of Texas System (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002042373	A1	20020411	
APPLICATION INFO.:	US 2001-909348	A1	20010719	(9)

	NUMBER	DATE

PRIORITY INFORMATION: US 2000-219800P 20000720 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 836
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Purification and characterization of the high affinity non-proteolytically activated (**NPAR**) thrombin receptor.
ACCESSION NUMBER: 2003:156453 BIOSIS
DOCUMENT NUMBER: PREV200300156453
TITLE: Purification and characterization of the high affinity non-proteolytically activated (**NPAR**) thrombin receptor.
AUTHOR(S): Bergmann, J. S. (1); Laird, A. C.; Tsulaia, T. V.; Keherly, M. J.; Carney, D. H.
CORPORATE SOURCE: (1) Human Biological Chemistry and Genetics, Medical Branch, University Texas, Galveston, TX, USA USA
SOURCE: Molecular Biology of the Cell, (Nov. 2002, 2002) Vol. 13, No. Supplement, pp. 290a. print.
Meeting Info.: 42nd Annual Meeting of the American Society for Cell Biology San Francisco, CA, USA December 14-18, 2002 American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Thrombin and thrombin peptide **TP508** (Chrysalin(R)) bind to a high affinity receptor that appears to be larger than known members of the proteolytically activated receptor (PAR) family.
ACCESSION NUMBER: 2002:165448 BIOSIS
DOCUMENT NUMBER: PREV200200165448
TITLE: Thrombin and thrombin peptide **TP508** (Chrysalin(R)) bind to a high affinity receptor that appears to be larger than known members of the proteolytically activated receptor (PAR) family.
AUTHOR(S): Bergmann, John S. (1); Laird, Aaron C.; Carney, Darrell H.
CORPORATE SOURCE: (1) Human Biological Chemistry and Genetics, University of Texas Medical Branch, 301 University Blvd., Galveston, TX, 77555 USA
SOURCE: Molecular Biology of the Cell, (Nov, 2001) Vol. 12, No. Supplement, pp. 330a. http://www.molbiolcell.org/. print.
Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology Washington DC, USA December 08-12, 2001
ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

bad date

L4 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2003 ACS
TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amt. of an agonist of the non-proteolytically activated thrombin receptor (**NPAR**) to the site. Also disclosed is a method of stimulating the proliferation and expansion of chondrocytes in vitro. The method comprises culturing chondrocytes in the presence of a stimulating amt. of an **NPAR** agonist. The **NPAR**

agonist **TP508** (a thrombin peptide deriv.) stimulated cartilage growth in rabbits.

ACCESSION NUMBER: 2002:89846 HCAPLUS
DOCUMENT NUMBER: 136:145245
TITLE: Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H.; Crowther, Roger S.; Stiernberg, Janet; Bergmann, John
PATENT ASSIGNEE(S): The Board of Regents, the University of Texas System, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002007748	A2	20020131	WO 2001-US22668	20010719
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002042373	A1	20020411	US 2001-909348	20010719
EP 1259598	A2	20021127	EP 2001-952846	20010719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002198154	A1	20021226	US 2002-50688	20020116

PRIORITY APPLN. INFO.:
US 2000-219800P P 20000720
US 2001-909348 A1 20010719
WO 2001-US22668 W 20010719

OTHER SOURCE(S): MARPAT 136:145245

```
=> s chondrocyte
L5       31685 CHONDROCYTE

=> d his

     (FILE 'HOME' ENTERED AT 16:00:18 ON 27 MAY 2003)

     FILE 'MEDLINE, USPATFULL, DGENE, EMBASE, FSTA, WPIDS, JICST-EPLUS,
     BIOBUSINESS, BIOSIS, HCAPLUS' ENTERED AT 16:01:01 ON 27 MAY 2003
L1           93 S NPAR OR NON-PROTEOLYTIC THROMBIN RECEPTOR
L2           55 S TP508
L3           11 S L1 AND AGONIST
L4            7 S L1 AND L2
L5        31685 S CHONDROCYTE

=> s l5 and l1
L6            9 L5 AND L1

=> d l6 ti abs ibib tot

L6   ANSWER 1 OF 9  USPATFULL
TI     Stimulation of cartilage growth with agonists of the non-proteolytically
       activated thrombin receptor
AB     Disclosed is a method of stimulating cartilage growth, repair or
```

regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an **NPAR** agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:344424 USPATFULL
TITLE:	Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S):	Carney, Darrell H., Dickinson, TX, UNITED STATES Crowther, Roger S., League City, TX, UNITED STATES Stiernberg, Janet, Paris, TX, UNITED STATES Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S):	Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002198154	A1	20021226
APPLICATION INFO.:	US 2002-50688	A1	20020116 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-909348, filed on 19 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS:	28
EXEMPLARY CLAIM:	1
LINE COUNT:	862

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 2 OF 9 USPATFULL

TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor

AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an **NPAR** agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:78716 USPATFULL
TITLE:	Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S):	Carney, Darrell H., Dickinson, TX, UNITED STATES Crowther, Roger S., League City, TX, UNITED STATES Stiernberg, Janet, Paris, TX, UNITED STATES Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S):	The Board of Regents, The University of Texas System (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002042373	A1	20020411
APPLICATION INFO.:	US 2001-909348	A1	20010719 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 836
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 3 OF 9 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of non-proteolytically activated thrombin receptor -
AN AAE20159 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an agonist of non-proteolytically activated thrombin receptor (**NPAR**). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of **NPAR** agonist to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is human thrombin peptide derivative which serves as a **NPAR** agonist.
ACCESSION NUMBER: AAE20159 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of non-proteolytically activated thrombin receptor -
INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Human thrombin peptide derivative #2.

L6 ANSWER 4 OF 9 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of non-proteolytically activated thrombin receptor -
AN AAE20158 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an agonist of non-proteolytically activated thrombin receptor (**NPAR**). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of **NPAR** agonist to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is human thrombin peptide derivative which serves as a **NPAR** agonist.
ACCESSION NUMBER: AAE20158 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of non-proteolytically activated thrombin receptor -

INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Human thrombin peptide derivative #1.

L6 ANSWER 5 OF 9 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of non-proteolytically activated thrombin receptor -
AN AAE20157 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an agonist of non-proteolytically activated thrombin receptor (**NPAR**). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of **NPAR** agonist to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is human thrombin peptide. The derivatives of thrombin peptide which serves as a **NPAR** agonist.
ACCESSION NUMBER: AAE20157 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of non-proteolytically activated thrombin receptor -
INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Human thrombin peptide.

L6 ANSWER 6 OF 9 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of non-proteolytically activated thrombin receptor -
AN AAE20156 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an agonist of non-proteolytically activated thrombin receptor (**NPAR**). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of **NPAR** agonist to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is serine esterase conserved peptide. This sequence is present in the thrombin peptide derivatives which serve as a **NPAR** agonist.
ACCESSION NUMBER: AAE20156 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of non-proteolytically activated thrombin receptor -
INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English

OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Serine esterase conserved peptide #2.

L6 ANSWER 7 OF 9 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of non-proteolytically activated thrombin receptor -
AN AAE20155 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an agonist of non-proteolytically activated thrombin receptor (**NPAR**). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of **NPAR** agonist to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is serine esterase conserved peptide. This sequence is present in the thrombin peptide derivatives which serve as a **NPAR** agonist.
ACCESSION NUMBER: AAE20155 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of non-proteolytically activated thrombin receptor -
INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Serine esterase conserved peptide #1.

L6 ANSWER 8 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Thrombin and thrombin peptide TP508 (Chrysalin(R)) bind to a high affinity receptor that appears to be larger than known members of the proteolytically activated receptor (PAR) family.
ACCESSION NUMBER: 2002:165448 BIOSIS
DOCUMENT NUMBER: PREV200200165448
TITLE: Thrombin and thrombin peptide TP508 (Chrysalin(R)) bind to a high affinity receptor that appears to be larger than known members of the proteolytically activated receptor (PAR) family.
AUTHOR(S): Bergmann, John S. (1); Laird, Aaron C.; Carney, Darrell H.
CORPORATE SOURCE: (1) Human Biological Chemistry and Genetics, University of Texas Medical Branch, 301 University Blvd., Galveston, TX, 77555 USA
SOURCE: Molecular Biology of the Cell, (Nov, 2001) Vol. 12, No. Supplement, pp. 330a. http://www.molbiolcell.org/. print. Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology Washington DC, USA December 08-12, 2001 ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

L6 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2003 ACS
TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amt. of an agonist of the non-proteolytically activated thrombin receptor (**NPAR**) to the site. Also disclosed is a method of stimulating the proliferation and expansion of chondrocytes in vitro. The method comprises culturing chondrocytes in the presence of

a stimulating amt. of an **NPAR** agonist. The **NPAR** agonist TP508 (a thrombin peptide deriv.) stimulated cartilage growth in rabbits.

ACCESSION NUMBER: 2002:89846 HCAPLUS
DOCUMENT NUMBER: 136:145245
TITLE: Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H.; Crowther, Roger S.; Stiernberg, Janet; Bergmann, John
PATENT ASSIGNEE(S): The Board of Regents, the University of Texas System, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002007748	A2	20020131	WO 2001-US22668	20010719
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002042373	A1	20020411	US 2001-909348	20010719
EP 1259598	A2	20021127	EP 2001-952846	20010719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002198154	A1	20021226	US 2002-50688	20020116

PRIORITY APPLN. INFO.:
US 2000-219800P P 20000720
US 2001-909348 A1 20010719
WO 2001-US22668 W 20010719

OTHER SOURCE(S): MARPAT 136:145245

```
=> s proteoglycan
L7       51610 PROTEOGLYCAN

=> d his

     (FILE 'HOME' ENTERED AT 16:00:18 ON 27 MAY 2003)

     FILE 'MEDLINE, USPATFULL, DGENE, EMBASE, FSTA, WPIDS, JICST-EPLUS,
     BIOBUSINESS, BIOSIS, HCAPLUS' ENTERED AT 16:01:01 ON 27 MAY 2003
L1           93 S NPAR OR NON-PROTEOLYTIC THROMBIN RECEPTOR
L2           55 S TP508
L3           11 S L1 AND AGONIST
L4            7 S L1 AND L2
L5        31685 S CHONDROCYTE
L6            9 S L5 AND L1
L7        51610 S PROTEOGLYCAN

=> s l1 and l7
L8           2 L1 AND L7

=> d l8 ti abs ibib tot

L8   ANSWER 1 OF 2  USPATFULL
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TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor

AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an **NPAR** agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:344424 USPATFULL		
TITLE:	Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor		
INVENTOR(S):	Carney, Darrell H., Dickinson, TX, UNITED STATES Crowther, Roger S., League City, TX, UNITED STATES Stiernberg, Janet, Paris, TX, UNITED STATES Bergmann, John, Galveston, TX, UNITED STATES		
PATENT ASSIGNEE(S):	Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002198154	A1	20021226
APPLICATION INFO.:	US 2002-50688	A1	20020116 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2001-909348, filed on 19 Jul 2001, PENDING		
	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)	
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133		
NUMBER OF CLAIMS:	28		
EXEMPLARY CLAIM:	1		
LINE COUNT:	862		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 2 OF 2 USPATFULL

TI Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor

AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an **NPAR** agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:78716 USPATFULL
TITLE:	Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S):	Carney, Darrell H., Dickinson, TX, UNITED STATES Crowther, Roger S., League City, TX, UNITED STATES Stiernberg, Janet, Paris, TX, UNITED STATES

	Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S):	The Board of Regents, The University of Texas System (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002042373	A1	20020411	
APPLICATION INFO.:	US 2001-909348	A1	20010719	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-219800P	20000720	(60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS:	21
EXEMPLARY CLAIM:	1
LINE COUNT:	836

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

[0032] As used herein, a therapeutically effective concentration is defined as a concentration of the particular agent which provides a satisfactory increase in the rate of repair or angiogenesis or which provides a satisfactory reduction or inhibition of restenosis or vascular occlusion. Again, such concentrations are believed to correspond to levels sufficient to elicit a stimulation of the high-affinity thrombin receptor in vitro. However, it is believed that the compositions will prove most effective when the stimulatory (agonistic) polypeptides are present at a concentration of from 0.1 .mu.M to 10 .mu.M.

[0033] For purposes of the present invention, a thrombin derivative is defined as any molecule with an amino acid sequence derived at least in part from that of thrombin, whether synthesized in vivo or in vitro. Accordingly, a thrombin derivative, as referred to herein, designates a polypeptide molecule which comprises fewer amino acids than thrombin.

[0034] A physiologically functional equivalent of a thrombin derivative encompasses molecules which differ from thrombin derivatives in particulars which do not affect the function of the thrombin receptor binding domain or the serine esterase conserved amino acid sequence. Such particulars may include, but are not limited to, conservative amino acid substitutions and modifications, for example, amidation of the carboxyl terminus, acetylation of the amino terminus, conjugation of the polypeptide to a physiologically inert carrier molecule, or sequence alterations in accordance with the serine esterase conserved sequences.

[0035] A thrombin receptor binding domain is defined as a polypeptide sequence which directly binds to the thrombin receptor and/or competitively inhibits binding between high-affinity thrombin receptors and alpha-thrombin.

[0036] A domain having a serine esterase conserved sequence comprises a polypeptide sequence containing at least 4-12 of the N-terminal amino acids of the dodecapeptide previously shown to be highly conserved among serine proteases (Asp-X.sub.1-Cys-X.sub.0.2-Gly-Asp-Ser-Gly-Gly-Pro-X.sub- .3-Val--SEQ ID NO. 5); wherein X.sub.1 is either Ala or Ser; X.sub.2 is either Glu or Gln; and X.sub.3 is either Phe, Met, Leu, His, or Val).

[0037] A stimulatory polypeptide is defined as a polypeptide derivative of thrombin, or a physiologically functional equivalent thereof, having the ability to both bind to and stimulate the thrombin receptor. Therefore, the stimulatory peptides will include both a thrombin receptor binding domain and a domain with a serine esterase conserved amino acid sequence.

[0038] The invention is illustrated by the following examples, which are not intended to be limiting in any way.

EXEMPLIFICATION

Example 1

TP508 Stimulates the Proliferation and Migration of Human Endothelial Cells In Vitro

[0039] To determine if TP508 could directly induce proliferation of endothelial cells, human microvascular endothelial cells were purchased from Clonetics, plated on tissue culture grade plastic in 24 well culture dishes and serum starved for 24 hours. Cells were stimulated in medium with or without TP508 for 48 hours, at which time proliferation was assessed using a direct cell count. As shown in FIG. 1, TP508 stimulated proliferation of microvascular endothelial cells by 30 to 50% over those treated in medium alone (1.0 .mu.g/ml TP508). This effect appeared to be specific since the growth of smooth muscle cells isolated from rat aorta was not affected by TP508.

[0040] TP508 effects on migration of human endothelial cells was assessed using an in vitro monolayer wound assay in which endothelial cells were plated in 35 mm culture dishes and allowed to grow to near confluency for three days, at which time the monolayer was "wounded" by scraping across the center of the dish with a rubber

policeman to remove a band of cells. Photographs were taken at this point, and the cells were then treated with fresh medium alone or medium containing various concentrations of TP508 and allowed to grow for an additional 48 hours. The cells were re-photographed, and the distance that the endothelial cells migrated into the wounded area was measured. As shown in FIG. 2, TP508 stimulated migration of endothelial cells, even when the cells were cultured on plastic alone.

[0041] These studies demonstrated that TP508 has direct angiogenic effects on human endothelial cells causing increased proliferation and migration in vitro. Additional studies indicate that exposure of endothelial cells to TP508 has a protective effect to prevent death of cells caused by oxidative exposure. This protective effect may also contribute to processes of re-endothelialization and angiogenesis.

Example 2

TP508 Stimulates Angiogenesis In Vitro in a Chorioalloantoic Membrane Model

[0042] Studies with full dermal surgical incisions and open excisional wounds in the backs of rats showed that a single topical application of TP508 stimulates revascularization and the patency of blood vessels traversing a surgical incision. Two surgical incisional wounds were made on the back of a rat. One wound was treated with a single application of TP508 (0.1 .mu.g); the other was untreated. Blood vessels were attracted to the treated wound rather than the control.

[0043] Addition of TP508 to agar disks placed on the chorioalloantoic membrane of chicken embryos resulted in an angiogenic outgrowth of blood vessels. Blood vessels were stimulated to grow into agar disks containing TP508. There was also an increase in collateral vessel outgrowth in vessels distal to the plug similar to that observed with other angiogenic factors.

Example 3

TP508 Showed Efficacy in Treating Myocardial Ischemia in a Porcine Model.

[0044] Yucatan minipigs had toroid shaped ameroid occluders placed on their proximal left circumflex arteries. The ameroid imbibed water over time, causing constriction of the vessel. Occlusion was verified four weeks after surgery by contrast enhanced angiography. At that time, each animal's chest was reopened, whereupon the region of ischemia was injected with a slow release formulation of TP508, i.e., TP508-containing PGLA microspheres, suspended in a Pluronic gel. The PLGA microspheres, which were prepared as described in Example 6, gave an initial burst release of drug (50% of load in 24 hours) and then displayed controlled release for another 3-4 days, by which time 80% of the load had been released. The gel used was 30% w/v Pluronic F68 in 0.9% saline. To each milliliter of gel, on ice to reduce the viscosity, 3.3 mg of PLGA microspheres were added immediately before injection. This gave a TP508 dose of 100 .mu.g/ml of gel, which was injected into ten sites (100 .mu.l per site) in the ischemic area. Controls received PLGA microspheres in Pluronic gel without TP508. Baseline, and post-treatment angiograms and echocardiograms were obtained.

[0045] Indices for myocardial wall thickening and cardiac ejection fraction showed trends that TP508 treated animals tolerated dobutamine-induced stress better than controls. After three weeks, the animals were evaluated with contrast enhanced echocardiography. Initial results on this limited number of animals demonstrated that TP508 treated animals under dobutamine stress had a slightly larger increase in ejection fraction and better maintained wall thickening compared to controls. Thus, this treatment appears to help restore functionality to the ischemic heart muscle.

Example 4

TP508 Stimulates Myocardial Revascularization in a Rabbit Model

[0046] TP508, formulated in sustained release PLGA microspheres, was injected into ischemic rabbit myocardium. An ameroid occluder was placed over the lateral division of the left main coronary artery of two rabbits just inferior to the A-V groove, as

described in Operschall et al., J. Appl. Physiol. 88:1438 (2000). Two weeks after placement, the animals' chests were reopened. In one animal, TP508 microspheres in pluronic gel (as described in Example 3) were injected into eight discrete locations within, and around, the area served by the occluded vessel. The other animal served as an untreated control. Approximately four weeks post-injection, the animals were sacrificed and their hearts fixed in 10% buffered formalin for 24 hours. Hearts were then sectioned across the area of interest and stained by hematoxylin-eosin and immunolabelled against Von Willebrand Factor (vWF), an endothelial cell marker.

[0047] Histology demonstrated that the control animal had significant fibrosis in the area served by the occluder. The TP508 treated heart, on the other hand, had healthy appearing myocardium with a larger number of functional capillaries with obvious red blood cells.

Example 5

TP508 Suppresses Restenosis in a Hypercholesterolemic Rabbit Model

[0048] This procedure was designed to provide a system for testing the efficacy of a Test Sample to inhibit neointimal formation and vascular occlusion following angioplasty in hypercholesterolemic New Zealand White Rabbits. The animals were fed a high fat diet consisting of 0.5% cholesterol and 2.0% peanut oil for 3 weeks. The animals were pretreated 24 hours prior to surgery; the iliac artery was injured with balloon angioplasty as described; and the animals were are treated with TP-508 for 7 days. The animals were maintained on a high fat diet for 4 weeks. Angiography was conducted prior to balloon angioplasty and at termination of the experiment. The injured and uninjured iliac arteries were harvested and prepared for histology. Morphometric measurements were made of the lumen, the neointima (if present), and the tunica media.

[0049] Test samples of TP-508 were dissolved/diluted in a sterile, pyrogen-free saline to the desired concentration and administered by intravenous injection in a 0.2 ml volume one day prior to surgery, the day of surgery, and for 6 successive days post surgery.

[0050] A 5 cm midline neck incision was made and the right carotid was exposed, proximately ligated, and incised. A 4 Fr Berman Balloon Angiographic Catheter was then introduced into the aorta. A 5 Fr sheath was introduced into the aorta via the 4 Fr Berman Balloon Angiographic Catheter. Three ml of blood was collected for cholesterol count. The rabbit was then injected with heparin and more anesthetics (if necessary). To visualize the iliac arteries, 6 ml of Hypaque 76% mixed with 4 ml sterile saline was injected through the catheter. Imaging was acquired of the iliac arteries (image is marked with grid and scissors are placed on the right side). The 4 Fr Berman Balloon Angiographic Catheter was removed from the sheath. A 0.014"/3.0 mm.times.20.0 mm/120 cm Balloon Catheter was then inserted through the sheath into the aorta and to the iliac artery. The balloon was inflated 3 times at 10 ATM for 30 seconds with 1 minute intervals. The catheter and sheath were then removed. The right carotid artery was ligated with 3.0 silk sutures. The neck incision was closed with PDS and the skin stapled and dressed with double antibiotic ointment.

[0051] The test sample(s) or control sample(s) were then administered to the rabbit. The Test Sample was diluted in the following manner: 0.3 ml of saline was drawn into a 1.0 ml syringe with a 23 G 1" needle. The volume was injected into the TP-508 vile. After the TP-508 dissolved, 0.25 ml of the solution was removed and administered. The cannulation tube was then flushed with saline. If the rabbit was a control, 0.2 ml of saline was injected and flushed with additional saline. The rabbit also received 0.3 ml of Buprenorphine via subcutaneous injection.

[0052] After surgery, the rabbit was allowed time to become alert while resting on the heating pad. The rabbit was then returned to his cage and allowed food and water ad libitum. The rabbits were maintained on the diet for 4 additional weeks until sacrifice.

[0053] Four weeks post-procedure, both iliac arteries were fixed in situ, harvested and prepared for histology. Digital images were then captured of the serial

histological sections spaced approximately one millimeter apart and morphometric measurements were made of the lumen, the neointima (if present) and the tunica media throughout the region of injury.

[0054] Histology Summary

[0055] Morphohistological analysis of 19 samples were completed using Image-Pro Plus and Excel software. Of the 19 samples, 2 demonstrated compromise of the external elastic lamina. One sample of the 19 appeared to require additional sectioning. Therefore, 16 samples were compared comprising 7 treated and 9 saline controls.

[0056] The thickness of the restenotic lesion was determined by measuring the area of the neointima via digital analysis. The tunica media of the vessels was measured similarly. These values were then normalized by summing the area of these two regions and dividing that result by the area of a normal (un-injured) media found within the same histological slide series. It was verified that there was no significant difference between groups in the areas found for the uninjured media.

[0057] When comparing treated animals against controls, the extent of restenosis was analyzed via three distinct methods: the "single worst value" method, the "average lesion thickness" method, and the "average of all sections" method. The "single worst value" method compares the maximum restenosis value obtained between operated vessels. The "average lesion thickness" method compares the averages all abnormal points within a well-defined region of injury between operated vessels. Lastly, the "average of all sections" method compares the average thickness of all samples measured, regardless of whether or not they appeared to be part of the lesion. The means of these results were tested for statistical significance via the Student's T-test.

[0058] Data Summary

[0059] All data analysis was completed using the two-tailed t-test assuming unequal variances. Alpha is 0.05 and the mean difference is assumed to be 0. Each analysis includes n=7 for treated and n=9 for saline control. The results are summarized in the following Table 1. The "difference" value shown relates to the percentage change of the treated as compared to the corresponding control. Values noted with an asterix were statistically significant.

1 TABLE 1

Technique: Measured Area:	Single Worst Value			Average Lesion Thickness			Average of All Sections		
	Treated	Controls	Diff.	Treated	Controls	Diff.	Treated	Controls	Diff.
Neointima	.202	.332	-39%*	.158	.245	-36%	.117	.185	-37%*
Media	.113	.133	-15%	.123	.152	-19%	.116	.140	-17%
Neo + Media/ Uninjured Media	4.56	7.73	-41%*	4.18	5.87	-29%*	3.49	5.55	-37%*

[0060] Conclusion

[0061] The data shows that TP-508 significantly suppressed restenosis and vascular

occlusion in the hypercholesterolemic rabbit model. This result is robust in that it is independent of the technique chosen for quantifying the results.

Example 6

Preparation of Polylactic Acid/Polyglycolic Acid Copolymer Microspheres of TP508

[0062] A double emulsion technique was used to prepare microspheres of polylactic acid/polyglycolic acid copolymer (PLA/PGA) containing TP508. Briefly, the matrix components were dissolved in methylene chloride and TP508 was dissolved in water. The two were gradually mixed together while vortexing to form a water-in-oil (W/O) emulsion. Polyvinyl alcohol (0.3% in water) was added to the emulsion with further vortexing to form the second emulsion (O/W), thereby forming a double emulsion: an O/W emulsion comprised of PLA/PGA droplets, and within those droplets, a second disperse phase consisting of TP508 in water. Upon phase separation, the PLA/PGA droplets formed discrete microspheres containing cavities holding TP508. To cause phase separation of the microspheres, a 2% isopropyl alcohol solution was added. The particles were collected by centrifugation, and then lyophilized to remove residual moisture. The composition of the matrix was varied to form microspheres with different release kinetics

2TABLE 2

Composition of different microsphere formulations
Polymer % % poly-ethylene
Formu-lation
PLA:PGA M. Wt. TP508 glycol

A 50:50 46,700 5 0
B
50:50 7,200 5 0
C 50:50 46,700 5 5
D 50:50 46,700 5 0

B 75:25 120,000 5 0

[0063] The mean diameter of the microspheres was measured in a Coulter counter and the drug entrapment efficiency was measured by spectrophotometric assay at 276 nm following dissolution of a weighed sample of microspheres in methylene chloride and extraction of the released drug into water (Table 3).

3TABLE 3

Formulation diameter and drug entrapment efficiency
Formulation Diameter, .mu.m TP508 Entrapment, %

A 26.0 53.8
B 16.2 27.1
C 17.6 58.9
D 23.9
42.6
B 25.8 36.2

[0064] To measure TP508 release from the different PLA/PGA matrices, 20 mg of microspheres were placed in 1.0 ml of PBS contained in 1.5 ml polypropylene microcentrifuge tubes. Tubes were incubated at 37.degree. C. and shaken at 60 rpm. At various times, the tubes were centrifuged and the supernatant containing released TP508 was removed and frozen for subsequent analysis. Fresh PBS was added to the microspheres and incubation was continued. TP508 in the supernatant was measured by absorbance at 276 nm. For each formulation, quadruplicate release determinations were performed. Formulations B and D showed no detectable drug release during 28 days of incubation at 37.degree. C. The remaining formulations all released detectable amounts of TP508, although in all cases the amount of drug released fell below detectable limits (<1 .mu.g/mg matrix/day) within 3-4 days. Formulations A and C showed the greatest release of TP508, releasing 60-80% of the entrapped drug over 3-4 days. The formulation with the fastest release kinetics, C, was chosen for further testing in in vivo studies described in Example 3 and Example 4.

[0065] While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS:

What is claimed is:

1. A method for promoting cardiac tissue repair comprising administering to the cardiac tissue a therapeutically effective amount of an angiogenic thrombin derivative peptide or a physiologically functional equivalent thereof.

2. The method according to claim 1 wherein said peptide comprises a thrombin receptor binding domain having the sequence Arg-Gly-Asp-Ala (SEQ ID NO. 1); and a serine esterase conserved sequence.

3. The method of claim 2 wherein the serine esterase conserved sequence comprises Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO. 2).

4. The method of claim 2 wherein the thrombin derivative peptide comprises the amino acid sequence: Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp--Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO. 3).

5. The method of claim 1 wherein the thrombin derivative peptide consists of the amino acid sequence Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-As-p-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO. 3).

6. The method of claim 1, wherein the cardiac tissue is administered a therapeutically effective amount of a physiologically equivalent thrombin derivative peptide comprising a C-terminal amide.

7. The method of claim 1, wherein the cardiac tissue is administered a therapeutically effective amount of a physiologically functional equivalent thrombin derivative peptide comprising Ala-Gly-Tyr-Lys-Pro-Asp--Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-CONH.- sub.2 (SEQ ID NO: 4).

8. The method of claim 1, wherein the cardiac tissue is administered a therapeutically effective amount of a physiologically functional equivalent thrombin derivative peptide consists of Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-G-ly-Gly-Pro-Phe-Val-CONH.sub.2 (SEQ ID NO: 4).

9. The method of claim 1 wherein the peptide is administered during or following cardiac surgery.

10. The method of claim 1 wherein the peptide is administered by injection into the cardiac tissue.

11. The method of claim 1 wherein a sustained release formulation comprising the angiogenic thrombin derivative peptide is administered to the cardiac tissue.

12. The method of claim 11 wherein the sustained release formulation is a polylactic acid/polyglycolic acid microparticles comprising the angiogenic thrombin derivative peptide or the physiologically functional equivalent thereof.

13. A method of stimulating revascularization comprising administering to cardiac tissue a therapeutically effective amount of an angiogenic thrombin derivative peptide or a physiologically functional equivalent thereof.

14. A method of stimulating vascular endothelial cell proliferation in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of an angiogenic thrombin derivative peptide or a physiologically functional equivalent thereof.

15. A method of inhibiting restenosis in a patient following balloon angioplasty, said method comprising administering to the patient a therapeutically effective amount of an angiogenic thrombin derivative peptide or a physiologically functional equivalent thereof.

16. The method of claim 15 wherein the peptide is coated onto a balloon angioplasty catheter.

17. The method of claim 15 wherein the peptide is administered systemically.

18. The method of claim 15 wherein the peptide is administered locally to a balloon induced damaged area of a blood vessel.

19. The method of claim 15 wherein a stent coated with the peptide is inserted into a blood vessel at a balloon induced damaged area.

20. The method of claim 15 wherein the peptide comprises a thrombin receptor binding domain having the sequence Arg-Gly-Asp-Ala (SEQ ID NO. 1); and a serine esterase conserved sequence.

21. The method of claim 20 wherein the serine esterase conserved sequence comprises Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO. 2).

22. The method of claim 20 wherein the thrombin derivative peptide comprises the amino acid sequence: Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Ar-
g-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO. 3).

23. The method of claim 15 wherein the thrombin derivative peptide consists of the amino acid sequence Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-A-
rg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO. 3).

24. The method of claim 15, wherein the patient is administered a therapeutically effective amount of a physiologically functional equivalent physiologically equivalent thrombin derivative peptide comprising a C-terminal amide.

25. The method of claim 15, wherein the patient is administered a therapeutically effective amount of a physiologically functional equivalent thrombin derivative peptide comprising Ala-Gly-Tyr-Lys-Pro-Asp-
-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-CONH.- sub.2 (SEQ ID NO: 4).

26. The method of claim 15, wherein the patient is administered a therapeutically effective amount of a physiologically functional equivalent thrombin derivative peptide consisting of
Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-G-
ly-Gly-Pro-Phe-Val-CONH.sub.2 (SEQ ID NO: 4).

27. A stent coated with an angiogenic thrombin derivative peptide or a physiologically functional equivalent thereof.

28. A method of inhibiting vascular occlusion in a patient, said method comprising administering to the patient a therapeutically effective amount of a thrombin derivative peptide or a physiologically functional equivalent thereof.

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ABSTRACT:

Disclosed is a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

GOVT-INTEREST:

[0002] The invention was supported, in whole or in part, by grant 1 R43 AR45508-01 and 2 R44 AR45508-02 from the National Institutes of Health. The Government has certain rights in the invention.

RELATED APPLICATIONS

[0001] This application is a continuation of U.S. application Ser. No. 09/909,122 filed Jul. 19, 2001 which claims the benefit of U.S. Provisional Application No. 60/219,300, filed Jul. 19, 2000, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0003] Mammalian bone tissue has a remarkable ability to regenerate and thereby repair injuries and other defects. For example, bone growth is generally sufficient to bring about full recovery from most simple and hairline fractures. Unfortunately, however, there are many injuries, defects or conditions where bone growth is inadequate to achieve an acceptable outcome. For example, bone regeneration generally does not occur throughout large voids or spaces. Therefore, fractures cannot heal unless the pieces are in close proximity. If a significant amount of bone tissue was lost as a result of the injury, the healing process may be incomplete, resulting in undesirable cosmetic and/or mechanical outcomes. This is often the case with non-union fractures or with bone injuries resulting from massive trauma. Tissue growth is also generally inadequate in voids and segmental gaps in bone caused, for example, by surgical removal of tumors or cysts. In other instances, it may be desirable to stimulate bone growth where bone is not normally found, i.e., ectopically. Spine fusion to relieve lower back pain where two or more vertebrae are induced to fuse is one example of desirable ectopic bone formation. Currently, such gaps or segmental defects require bone grafts for successful repair or gap filling. The development of effective bone graft substitutes would eliminate the need to harvest bone from a second surgical site for a graft procedure, thereby significantly reducing the discomfort experienced by the patient and risk of donor site healing complications.

[0004] Compounds which stimulate or induce bone growth at sites where such growth would not normally occur if left untreated are said to be "osteoinductive". An osteoinductive compound would have great value as a drug to treat the conditions described above. A number of osteoinductive proteins have been identified, isolated and expressed using recombinant technology. Examples include the bone morphogenic proteins (BMPs) disclosed in U.S. Pat. No. 5,902,705 and WO 95/16035. However, the use of recombinant proteins as therapeutic agents generally has a number of drawbacks, including the cost of manufacture, in vivo biodegradation and short shelf lives. Consequently, scientists are continuing to search for new osteoinductive agents which do not have the aforementioned shortcomings.

SUMMARY OF THE INVENTION

[0005] It has now been found that compounds which activate the non-proteolytic thrombin receptor are osteoinductive. For example, the compound TP508, an agonist of the non-proteolytic thrombin receptor, stimulates bone growth in segmental critical size defects created in the ulna of male New Zealand rabbits (Example 2). As shown by x-ray and confirmed by histology and mechanical testing, there was a significant increase in bone formation induced by TP508 at doses of 100 .mu.g and 200 .mu.g compared with untreated controls. Based on these results, novel methods of stimulating bone growth in a subject and novel implantable pharmaceutical compositions are disclosed herein.

[0006] One embodiment of the present invention is a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site.

[0007] Another embodiment of the present invention is a pharmaceutical composition comprising an implantable, biocompatible carrier and an agonist of the non-proteolytically activated thrombin receptor.

[0008] The method of the present invention is directed at stimulating bone growth in a subject and can be used at sites where bone growth would not occur, absent treatment with autologous bone grafts or administration of bone growth factors. The method involves the administration of agonists of the non-proteolytic thrombin receptor. Such agonists include small peptides and physiologically functional equivalents having homology to the segment between amino acid 508 and 530 of human prothrombin. These small peptides are inexpensive to prepare in bulk quantities and are osteoinductive at low dose. In addition, their lyophilized form is stable for at least thirty months when stored at 5.degree. C. and at 60% relative humidity.

DETAILED DESCRIPTION OF THE INVENTION

[0009] "Osteoinduction" refers to stimulating bone growth at a site within a subject at which little or no bone growth would occur if the site were left untreated. Sites which could therapeutically benefit from the induction of bone growth are referred to as "in need of osteoinduction". Examples include non-union fractures or other severe or massive bone trauma. It is noted that bone growth normally occurs at bone injuries such as simple or hairline fractures and well opposed complex fractures with minimal gaps without the need for further treatment. Such injuries are not considered to be "in need of osteoinduction".

[0010] Simple fracture repair appears to be quite different from the induction of bone formation required to fill non-union fractures, segmental gaps or bone voids caused, for example, by removal of a bone tumor or cyst. These cases require bone grafting or induction of new bone growth generally employing some type of matrix or scaffolding to serve as a bone growth substitute. Induced bone growth can also be therapeutically beneficial at certain sites within a subject (referred to as "ectopic" sites) where bone tissue would not normally be found, such as a site in need of a bone graft or bone fusion. Fusions are commonly used to treat lower back pain by physically coupling one or more vertebrae to its neighbor. The bone created by such a fusion is located at a site not normally occupied by bone tissue. Osteoinduction at these ectopic sites can act as a "graft substitute" whereby induced bone growth between the vertebrae takes the place of a graft and obviates the need for a second operation to harvest bone for the grafting procedure. Induction of bone growth is also needed for treating acquired and congenital craniofacial and other skeletal or dental anomalies (see e.g., Glowacki et al., Lancet 1: 959 (1981)); performing dental and periodontal reconstructions where lost bone replacement or bone augmentation is required such as in a jaw bone; and supplementing alveolar bone loss resulting from periodontal disease to delay or prevent tooth loss (see e.g., Sigurdsson et al., J. Periodontol., 66: 511(1995)).

[0011] Applicants have discovered that compounds which stimulate or activate the non-proteolytically activated thrombin receptor (hereinafter "NPAR") are osteoinductive. Such compounds are said to be NPAR agonists. NPAR is a high-affinity thrombin receptor present on the surface of most cells. This NPAR component is largely responsible for high-affinity binding of thrombin, proteolytically inactivated thrombin, and thrombin derived peptides to cells. NPAR appears to mediate a number of cellular signals that are initiated by thrombin independent of its proteolytic activity. An example of one such signal is the upregulation of annexin V and other molecules identified by subtractive hybridization (see Sower, et. al., Experimental Cell Research 247:422 (1999)). NPAR is therefore characterized by its high affinity interaction with thrombin at cell surfaces and its activation by proteolytically inactive derivatives of thrombin and thrombin derived peptide agonists as described below. NPAR activation can be assayed based on the ability of molecules to stimulate cell proliferation when added to fibroblasts in the presence of submitogenic concentrations of thrombin or molecules that activate protein kinase C or compete with .sup.125I-thrombin for high affinity binding to thrombin receptors, as disclosed in U.S. Pat. Nos. 5,352,664 and 5,500,412 and in Glenn et al., J. Peptide Research 1:65 (1988). NPAR is to be distinguished from other thrombin binding proteins and the cloned family of proteolytically-activated receptors for thrombin, including the receptors PAR1, PAR2, PAR3 and PAR4. PAR1 possesses a specific thrombin cleavage site that allows thrombin cleavage to expose a new amino-terminus domain that acts as a tethered ligand folding back onto itself inducing its activation (see, Vu, et al., Cell. 64:1057 (1991)). PAR2 has a similar

mechanism for activation, but is principally activated by trypsin-like enzymes (see, Zhong, et al., J. Biol. Chem. 267:16975 (1992)). PAR3 also has a similar mechanism of activation and appears to function as a second thrombin receptor in platelets (see, Ishihara, et al., Nature. 386:502 (1997)). PAR4 has been detected in mouse megakaryocytes and studies suggest that it also functions in human platelets (see, Kahn, et al., Nature 394:690 (1998)). In contrast with these PAR receptors, activation of NPAR requires no proteolytic cleavage.

[0012] Several lines of evidence indicate that NPAR is distinct from PAR receptors: (1) a population of cells has been isolated that express fully functional PAR1 receptors, but are non-responsive to thrombin due to a defect in the NPAR signal transduction pathway (see, Kim, et al., J. Cell. Physiol. 160:573 (1994)); (2) neutrophils bind.sup.125I thrombin with high affinity and their chemotaxis is stimulated by proteolytically inactivated thrombin or NPAR agonists (see, Ramakrishnan and Carney, Mol. Biol. Cell 4:1993 (1993)), yet they do not express PAR1 (see Jenkins, et al., J. Cell Sci. 108:3059 (1995)); (3) IIC9 fibroblasts over-express PAR1 , but do not bind thrombin with high affinity (see, Kim, D. Ph.D. Dissertation. The University of Texas Medical Branch at Galveston, 1995; and Low, et al., "Cancer Cells 3/Growth Factors and Transformation", Cold Spring Harbor Laboratory, New York); and (4) NPAR agonists have distinct effects on gene expression from those of the PAR receptor agonist peptides (see, Sower, et. al., Experimental Cell Research 247: 422 (1999).

[0013] One example of an NPAR agonist is a thrombin peptide derivative, i.e., a polypeptide with no more than about fifty amino acids, preferably no more than about thirty amino acids and having sufficient homology to the fragment of human thrombin corresponding to prothrombin amino acids 508-530 (SEQ ID NO. 5) that the polypeptide activates NPAR. The thrombin peptide derivatives described herein preferably have between about 12 and 23 amino acids, more preferably between about 19 and 23 amino acids. One example of a thrombin peptide derivative comprises a moiety represented by Structural Formula (I):

Asp-Ala-R (I)

[0014] R is a serine esterase conserved domain. Serine esterases, e.g., trypsin, thrombin chymotrypsin and the like, have a region that is highly conserved. "Serine esterase conserved domain" refers to a polypeptide having the amino acid sequence of one of these conserved regions or is sufficiently homologous to one of these conserved regions such that the thrombin peptide derivative retains NPAR activating ability.

[0015] A physiologically functional equivalent of a thrombin peptide derivative encompasses molecules which differ from thrombin derivatives in particulars which do not affect the function of the thrombin receptor binding domain or the serine esterase conserved amino acid sequence. Such particulars may include, but are not limited to, conservative amino acid substitutions and modifications, for example, amidation of the carboxyl terminus, acetylation of the amino terminus, conjugation of the polypeptide to a physiologically inert carrier molecule, or sequence alterations in accordance with the serine esterase conserved sequences.

[0016] A thrombin receptor binding domain is defined as a polypeptide which directly binds to the thrombin receptor and/or competitively inhibits binding between high-affinity thrombin receptors and alpha thrombin. In one embodiment, the serine esterase conserved sequence has the amino acid sequence of SEQ ID NO. 1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-- Phe-Val) or a C-terminal truncated fragment of a polypeptide having the amino acid sequence of SEQ ID NO 1. It is understood, however, that zero, one, two or three amino acids in the serine esterase conserved sequence can differ from the corresponding amino acid in SEQ ID NO 1. Preferably, the amino acids in the serine esterase conserved sequence which differ from the corresponding amino acid in SEQ ID NO 1 are conservative substitutions, and are more preferably highly conservative susbstitutions. A "C-terminal truncated fragment" refers to a fragment remaining after removing an amino acid or block of amino acids from the C-terminus, said fragment having at least six and more preferably at least nine amino acids.

[0017] More preferably, the serine esterase conserved sequence has the amino acid sequence of SEQ ID NO 2 (Cys-X.sub.1-Gly-Asp-Ser-Gly-Gly-Pro-X- .sub.2-Val; X.sub.1 is Glu or Gln and X.sub.2 is Phe, Met, Leu, His or Val) or a C-terminal truncated fragment thereof having at least six amino acids, preferably at least nine amino acids.

[0018] In a preferred embodiment, the thrombin peptide derivative comprises a serine esterase conserved sequence and a polypeptide having a more specific thrombin amino acid sequence Arg-Gly-Asp-Ala (SEQ ID NO 3). One example of a thrombin peptide derivative of this type comprises Arg-Gly-Asp-Ala-Cys-X.sub.1-Gly-Asp-Ser-Gly-Gly-Pro-X.sub.2-Val (SEQ ID NO 4). X.sub.1 and X.sub.2 are as defined above. When the thrombin peptide derivative comprises SEQ ID NO 4, it preferably has the amino acid sequence of SEQ ID NO 5 (Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly- -Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val) or an N-terminal truncated fragment thereof, provided that zero, one, two or three amino acids at positions 1-9 in the thrombin peptide derivative differ from the amino acid at the corresponding position of SEQ ID NO 5. Preferably, the amino acids in the thrombin peptide derivative which differ from the corresponding amino acid in SEQ ID NO 5 are conservative substitutions, and are more preferably highly conservative susbstitutions. An "N-terminal truncated fragment" refers to a fragment remaining after removing an amino acid or block of amino acids from the N-terminus, preferably a block of no more than six amino acids, more preferably a block of no more than three amino acids. A physiologically functional equivalent of SEQ ID NO: 5 is SEQ ID NO: 6 which has the identical amino sequence of SEQ ID NO: 5 and also contains a C-terminal amide.

[0019] TP508 is an example of a thrombin peptide derivative and has the amino acid sequence of SEQ ID NO 5.

[0020] A "conservative substitution" is the replacement of an amino acid with another amino acid that has the same net electronic charge and approximately the same size and shape. Amino acids with aliphatic or substituted aliphatic amino acid side chains have approximately the same size when the total number carbon and heteroatoms in their side chains differs by no more than about four. They have approximately the same shape when the number of branches in the their side chains differs by no more than one. Amino acids with phenyl or substituted phenyl groups in their side chains are considered to have about the same size and shape. Listed below are five groups of amino acids. Replacing an amino acid in a polypeptide with another amino acid from the same group results in a conservative substitution:

[0021] Group I: glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, and non-naturally occurring amino acids with C1-C4 aliphatic or C1-C4 hydroxyl substituted aliphatic side chains (straight chained or monobranched).

[0022] Group II: glutamic acid, aspartic acid and non-naturally occurring amino acids with carboxylic acid substituted C1-C4 aliphatic side chains (unbranched or one branch point).

[0023] Group III: lysine, ornithine, arginine and non-naturally occurring amino acids with amine or guanidino substituted C1-C4 aliphatic side chains (unbranched or one branch point).

[0024] Group IV: glutamine, asparagine and non-naturally occurring amino acids with amide substituted C1-C4 aliphatic side chains (unbranched or one branch point).

[0025] Group V: phenylalanine, phenylglycine, tyrosine and tryptophan.

[0026] A "highly conservative substitution" is the replacement of an amino acid with another amino acid that has the same functional group in the side chain and nearly the same size and shape. Amino acids with aliphatic or substituted aliphatic amino acid side chains have nearly the same size when the total number carbon and heteroatoms in their side chains differs by no more than two. They have nearly the same shape when they have the same number of branches in the their side chains. Example of highly conservative substitutions include valine for leucine, threonine

for serine, aspartic acid for glutamic acid and phenylglycine for phenylalanine. Examples of substitutions which are not highly conservative include alanine for valine, alanine for serine and aspartic acid for serine.

[0027] Other NPAR agonists include small organic molecules which bind and activate NPAR. Agonists of this type can be conveniently identified with high through-put screening, e.g., with assays that assess the ability of molecules to stimulate cell proliferation when added to fibroblasts in the presence of submitogenic concentrations of thrombin or molecules that activate protein kinase C as disclosed in U.S. Pat. Nos. 5,352,664 and 5,500,412. The entire teachings for U.S. Pat. Nos. 5,352,664 and 5,500,412 are incorporated herein by reference.

[0028] The term "NPAR agonist" also includes compounds and combinations of compounds known to activate NPAR. Examples are disclosed in U.S. Pat. Nos. 5,352,664 and 5,500,412 and include the combination of DIP-alpha-thrombin with phorbol myristate acetate.

[0029] An implantable biocompatible carrier for use in the pharmaceutical compositions described herein functions as a suitable delivery or support system for the NPAR agonist. A biocompatible carrier should be non-toxic, non-inflammatory, non-immunogenic and devoid of other undesired reactions at the implantation site. Suitable carriers also provide for release of the active ingredient and preferably for a slow, sustained release over time at the implantation site.

[0030] Suitable carriers include porous matrices into which bone progenitor cells may migrate. Osteogenic cells can often attach to such porous matrices, which can then serve as a scaffolding for bone and tissue growth. For certain applications, the carrier should have sufficient mechanical strength to maintain its three dimensional structure and help support the immobilization of the bone segments being united or grafted together. Porous matrices which provide scaffolding for tissue growth can accelerate the rate of bone growth and are said to be "osteoconductive". Osteoconductive carriers are highly preferred for use in the pharmaceutical compositions described herein.

[0031] Examples of suitable osteoconductive carriers include collagen (e.g., bovine dermal collagen), fibrin, calcium phosphate ceramics (e.g., hydroxyapatite and tricalcium phosphate), calcium sulfate, guanidine-extracted allogenic bone and combinations thereof. A number of suitable carriers are commercially available, such as COLLOGRAFT (Collagen Corporation, Palo Alto, Calif.), which is a mixture of hydroxyapatite, tricalcium phosphate and fibrillar collagen, and INTERPORE (Interpore International, Irvine Calif.), which is a hydroxyapatite biomatrix formed by the conversion of marine coral calcium carbonate to crystalline hydroxyapatite.

[0032] A number of synthetic biodegradable polymers can serve as osteoconductive carriers with sustained release characteristics. Descriptions of these polymers can be found in Behravesh et al., Clinical Orthopaedics 367:S118 (1999) and Lichun et al., Polymeric Delivery Vehicles for Bone Growth Factors in "Controlled Drug Delivery-Designing Technologies for the Future" Park and Mrsny eds., American Chemical Society, Washington, D.C. (2000). The entire teachings of these references are incorporated herein by reference. Examples of these polymers include poly a-hydroxy esters such as polylactic acid/polyglycolic acid homopolymers and copolymers, polyphosphazenes (PPHOS), polyanhydrides and poly(propylene fumarates).

[0033] Polylactic acid/polyglycolic acid (PLGA) homo and copolymers are well known in the art as sustained release vehicles. The rate of release can be adjusted by the skilled artisan by variation of polylactic acid to polyglycolic acid ratio and the molecular weight of the polymer (see Anderson, et al., Adv. Drug Deliv. Rev. 28:5 (1997), the entire teachings of which are incorporated herein by reference). The incorporation of poly(ethylene glycol) into the polymer as a blend to form microparticle carriers allows further alteration of the release profile of the active ingredient (see Cleek et al., J. Control Release 48:259 (1997), the entire teachings of which are incorporated herein by reference). Ceramics such as calcium phosphate and hyroxyapatite can also be incorporated into the formulation to improve mechanical qualities.

[0034] PPHOS polymers contain alternating nitrogen and phosphorous with no carbon in the polymer backbone, as shown below in Structural Formula (II): 1

[0035] The properties of the polymer can be adjusted by suitable variation of side groups R and R' that are bonded to the polymer backbone. For example, the degradation of and drug release by PPHOS can be controlled by varying the amount of hydrolytically unstable side groups. With greater incorporation of either imidazolyl or ethylglycol substituted PPHOS, for example, an increase in degradation rate is observed (see Laurencin et al., J. Biomed Mater. Res. 27:963 (1993), the entire teachings of which are incorporated herein by reference), thereby increasing the rate of drug release.

[0036] Polyanhydrides, shown in Structural Formula (III), have well defined degradation and release characteristics that can be controlled by including varying amounts of hydrophobic or hydrophilic monomers such as sebacic acid and 1,3-bis(p-carboxyphenoxy)propane (see Leong et al., J. Biomed. Mater. Res. 19:941 (1985), the entire teachings of which are incorporated herein by reference). To improve mechanical strength, anhydrides are often copolymerized with imides to form polyanhydride-co-imides. Examples of polyanhydride-co-imides that are suitable for orthopaedic applications are poly(trimellitylimido-glycine-co-1,6-bis(carboxyphenoxy)hexane and pyromellityimidoalanine: 1,6-bis(p-carboxyphenoxy)hexane copolymers. 2

[0037] Poly(propylene fumarates) (PPF) are highly desirable biocompatible implantable carriers because they are an injectable, in situ polymerizable, biodegradable material. "Injectable" means that the material can be injected by syringe through a standard needle used for injecting pastes and gels. PPF, combined with a vinyl monomer (N-vinyl pyrrolidinone) and an initiator (benzoyl peroxide

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L2	TP508 and agonist	8	L2
L1	jp-10316581$.did.	2	L1

END OF SEARCH HISTORY

[0002] The invention was supported, in whole or in part, by grant 1 R43 AR46343-01 from the National Institutes of Health/National Institute of Arthritis and Muscoskeletal and Skin Diseases. The Government has certain rights in the invention.

RELATED APPLICATIONS

[0001] This application is a continuation of U.S. application Ser. No. 09/909,348 filed Jul. 19, 2001, which claims the benefit of U.S. Provisional Application No. 60/219,800, filed Jul. 20, 2000, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0003] Unlike most tissues, cartilage does not self-repair following injury. Cartilage is an avascular tissue made up largely of cartilage specific cells, the chondrocytes, special types of collagen, and proteoglycans. The inability of cartilage to self-repair after injury, disease, or surgery is a major limiting factor in rehabilitation of degrading joint surfaces and injury to meniscal cartilage. Osteoarthritis, the major degenerative disease of weight bearing joint surfaces, is caused by eroding or damaged cartilage surfaces and is present in approximately 25% of the over 50-year-old population. In the US more than 20 million people suffer from osteoarthritis, with annual healthcare costs of more than $8.6 billion. In addition, the cost for cartilage repair from acute joint injury (meniscal lesions, patellar surface damage and chondromalacia) exceeds $1 billion annually. Therefore, new therapeutic approaches are needed to heal lesions of cartilage caused by degeneration or acute trauma.

SUMMARY OF THE INVENTION

[0004] It has now been found that chondrocytes isolated from articular cartilage respond to compounds which activate the non-proteolytic thrombin cell surface receptor (hereinafter "NPAR"). For example, chondrocytes express approximately 233,000 thrombin binding sites per cell with apparent affinities of approximately 0.1 nM (3000 sites) and 27 nM (230,000 sites) (Example 1). In addition, the compound TP508, an agonist of the non-proteolytic thrombin receptor, stimulates proliferation of bovine chondrocytes in culture in the presence of thrombin as a co-mitogen (Example 2A) and stimulates by itself the proliferation of rat chondrocytes cultured in three dimensional matrix culture (Example 3A). This same TP508 compound also stimulates proteoglycan synthesis as measured by the incorporation of .sup.35S sulfate in both bovine chondrocytes (Example 2B) and 3-dimensional cultures of rat chondrocytes (Example 3B). These in vitro experiments demonstrate that NPAR agonists can stimulate proliferation and matrix production in chondrocytes isolated from articular cartilage. Additional in vivo experiments demonstrate that delivering TP508 in a sustained release formulation to rabbit trochlear grove cartilage defects which extend into the subchondral bone results in repair of the cartilage defect, including repair of subchondral bone, restoration of a normal cartilage surface and integration of the newly formed cartilage with uninjured cartilage outside of the defect area (Example 5).

[0005] Based on the results reported in the prior paragraph, novel methods of stimulating chondrocyte growth in vivo and cartilage repair in a subject and novel delivery methods for delivering pharmaceutical compositions to articular defects to aid in surface repair and to prevent articular degradation are disclosed herein.

[0006] The present invention is a method of stimulating cartilage growth, regeneration or repair at a site in a subject where cartilage growth, repair or regeneration is needed. The method comprises the step of administering a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor to the site of injury.

[0007] Another embodiment of the present invention is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an NPAR agonist.

DETAILED DESCRIPTION OF THE INVENTION

[0008] Sites in need of cartilage growth, repair or regeneration are found in subjects with osteoarthritis. Osteoarthritis or degenerative joint disease is a slowly progressive, irreversible, often monoarticular disease characterized by pain and loss of function. The underlying cause of the pain and debilitation is the cartilage degradation that is one of the major symptoms of the disease. Hyaline cartilage is a flexible tissue that covers the ends of bones and lies between joints such as the knee. It is also found in between the bones along the spine. Cartilage is smooth, allowing stable, flexible movement with minimal friction, but is also resistant to compression and able to distribute applied loads. As osteoarthritis progresses, surfaces of cartilage and exposed underlying bone become irregular. Instead of gliding smoothly, boney joint surfaces rub against each other, resulting in stiffness and pain. Regeneration of damaged cartilage and the growth of new cartilage at these arthritic sites would relieve the pain and restore the loss of function associated with osteoarthritis.

[0009] Cartilage damage can also occur from trauma resulting from injury or surgery. Sports injuries are a common cause of cartilage damage, particularly to joints such as the knee. Traumatic injury to cartilage can result in the same type of functional impairment. Therefore, sites in a subject with cartilage that has been damaged by trauma or disease are in need of treatment to restore or promote the growth of cartilage.

[0010] Applicants have discovered that compounds which stimulate or activate the non-proteolytically activated thrombin receptor (hereinafter "NPAR") can stimulate chondrocytes to proliferate. Chondrocytes are cells which make up about 1% of the volume of cartilage and which replace degraded matrix molecules to maintain the correct volume and mechanical properties of the tissue. Applicants have also found that compounds which stimulate or activate NPAR stimulate proteoglycan synthesis in chondrocytes. Proteoglycan is a major cartilage component. Based on these results, Applicants delivered the NPAR agonist TP508, prepared in a sustained release formulation, to defects in rabbit trochlear grove cartilage and discovered that the peptide stimulated repair of the defect that included formation of new cartilage with a normal cartilage surface. The peptide also stimulated layering and integration of this new cartilage into adjacent, uninjured cartilage and restoration of the subchondral bone. It is concluded that NPAR agonists can induce cartilage growth and repair when administered to sites needing cartilage growth and/or repair.

[0011] Compounds which stimulate or activate NPAR are said to be NPAR agonists. NPAR is a high-affinity thrombin receptor present on the surface of most cells. NPAR is largely responsible for high-affinity binding of thrombin, proteolytically inactivated thrombin, and thrombin derived peptides to cells. NPAR agonists and antagonists can compete for the affinity binding with thrombin to cells (see, e.g., Glenn et al., J. Peptide Research 1:65 (1988)). NPAR appears to mediate a number of cellular signals that are initiated by thrombin independent of its proteolytic activity. An example of one such signal is the upregulation of annexin V and other molecules identified by subtractive hybridization (see Sower, et. al., Experimental Cell Research 247:422 (1999)). NPAR is therefore characterized by its high affinity interaction with thrombin at cell surfaces and its activation by proteolytically inactive derivatives of thrombin and thrombin derived peptide agonists as described below. NPAR activation can be assayed based on the ability of its agonists to stimulate cell proliferation when added to fibroblasts in the presence of submitogenic concentrations of thrombin or molecules that activate protein kinase C as disclosed in U.S. Pat. Nos. 5,352,664 and 5,500,412.

[0012] NPAR is to be distinguished from other thrombin binding proteins and the cloned family of proteolytically-activated receptors for thrombin, including the receptors PAR1, PAR2, PAR3 and PAR4. PAR1 possesses a specific thrombin cleavage site that allows thrombin cleavage to expose a new amino-terminus domain that acts as a tethered ligand folding back onto itself inducing its activation (see, Vu, et al., Cell. 64:1057 (1991)). PAR2 has a similar mechanism for activation, but is principally activated by trypsin-like enzymes (see, Zhong, et al., J. Biol. Chem. 267:16975 (1992)). PAR3 also has a similar mechanism of activation and appears to function as a second thrombin receptor in platelets (see, Ishihara, et al., Nature. 386:502 (1997)). PAR4 has been detected in mouse megakaryocytes and studies suggest

that it also functions in human platelets (see, Kahn, et al., Nature 394:690 (1998)). In contrast with these PAR receptors, activation of NPAR requires no proteolytic cleavage.

[0013] Several lines of evidence indicate that NPAR is distinct from PAR receptors: (1) a population of cells has been isolated that express fully functional PAR1 receptors, but are non-responsive to thrombin due to a defect in the NPAR signal transduction pathway (see, Kim, et al., J. Cell. Physiol. 160:573 (1994)); (2) neutrophils bind .sup.125I thrombin with high affinity and their chemotaxis is stimulated by proteolytically inactivated thrombin or NPAR agonists (see, Ramakrishnan and Carney, Mol. Biol. Cell 4:1993 (1993)), yet they do not express PAR1 (see Jenkins, et al., J. Cell Sci. 108:3059 (1995)); (3) IIC9 fibroblasts over-express PAR1, but do not bind thrombin with high affinity (see, Kim, D. Ph.D. Dissertation. The University of Texas Medical Branch at Galveston, 1995; and Low, et al., "Cancer Cells 3/Growth Factors and Transformation", Cold Spring Harbor Laboratory, New York); and (4) NPAR agonists have distinct effects on gene expression from those of the PAR receptor agonist peptides (see, Sower, et. al., Experimental Cell Research 247: 422 (1999).

[0014] One example of an NPAR agonist is a thrombin peptide derivative and physiologically functional equivalents, i.e., a polypeptide with no more than about fifty amino acids, preferably no more than about thirty amino acids and having sufficient homology to the fragment of human thrombin corresponding to prothrombin amino acids 508-530 (SEQ ID NO. 5) that the polypeptide activates NPAR. The thrombin peptide derivatives described herein preferably have between about 12 and 23 amino acids, more preferably between about 19 and 23 amino acids. One example of a thrombin peptide derivative comprises a moiety represented by Structural Formula (I):

Asp-Ala-R (I)

[0015] R is a serine esterase conserved domain. Serine esterases, e.g., trypsin, thrombin, chymotrypsin and the like, have a region that is highly conserved. "Serine esterase conserved domain" refers to a polypeptide having the amino acid sequence of one of these conserved regions or is sufficiently homologous to one of these conserved regions such that the thrombin peptide derivative retains NPAR activating ability.

[0016] A physiologically functional equivalent of a thrombin derivative encompasses molecules which differ from thrombin derivatives in particulars which do not affect the function of the thrombin receptor binding domain or the serine esterase conserved amino acid sequence. Such particulars may include, but are not limited to, conservative amino acid substitutions and modifications, for example, amidation of the carboxyl terminus, acetylation of the amino terminus, conjugation of the polypeptide to a physiologically inert carrier molecule, or sequence alterations in accordance with the serine esterase conserved sequences.

[0017] A thrombin receptor binding domain is defined as a polypeptide which directly binds to the thrombin receptor and/or competitively inhibits binding between high-affinity thrombin receptors and alpha thrombin.

[0018] In one embodiment, the serine esterase conserved sequence has the amino acid sequence of SEQ ID NO. 1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-- Val) or a C-terminal truncated fragment of a polypeptide having the amino acid sequence of SEQ ID NO 1. It is understood, however, that zero, one, two or three amino acids in the serine esterase conserved sequence can differ from the corresponding amino acid in SEQ ID NO 1. Preferably, the amino acids in the serine esterase conserved sequence which differ from the corresponding amino acid in SEQ ID NO 1 are conservative substitutions, and are more preferably highly conservative substitutions. A "C-terminal truncated fragment" refers to a fragment remaining after removing an amino acid or block of amino acids from the C-terminus, said fragment having at least six and more preferably at least nine amino acids.

[0019] More preferably, the serine esterase conserved sequence has the amino acid sequence of SEQ ID NO 2 (Cys-X.sub.1-Gly-Asp-Ser-Gly-Gly-Pro-X- .sub.2-Val; X.sub.1

is Glu or Gln and X.sub.2 is Phe, Met, Leu, His or Val) or a C-terminal truncated fragment thereof having at least six amino acids, preferably at least nine amino acids.

[0020] In a preferred embodiment, the thrombin peptide derivative comprises a serine esterase conserved sequence and a polypeptide having a more specific thrombin amino acid sequence Arg-Gly-Asp-Ala (SEQ ID NO 3). One example of a thrombin peptide derivative of this type comprises Arg-Gly-Asp-Ala-Cys-X.sub.1-Gly-Asp-Ser-Gly-Gly-Pro-X.sub.2-Val (SEQ ID NO 4). X.sub.1 and X.sub.2 are as defined above. When the thrombin peptide derivative comprises SEQ ID NO 4, it preferably has the amino acid sequence of SEQ ID NO 5 (Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-
-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val) or an N-terminal truncated fragment thereof, provided that zero, one, two or three amino acids at positions 1-9 in the thrombin peptide derivative differ from the amino acid at the corresponding position of SEQ ID NO 5. Preferably, the amino acids in the thrombin peptide derivative which differ from the corresponding amino acid in SEQ ID NO 5 are conservative substitutions, and are more preferably highly conservative susbstitutions. An "N-terminal truncated fragment" refers to a fragment remaining after removing an amino acid or block of amino acids from the N-terminus, preferably a block of no more than six amino acids, more preferably a block of no more than three amino acids.

[0021] TP508 is an example of a thrombin peptide derivative and has the amino acid sequence of SEQ ID NO 5. A physiologically functional equivalent of SEQ ID NO: 5 is SEQ ID NO: 6 which has the identical amino sequence of SEQ ID NO: 5 and also contains a C-terminal amide.

[0022] A "conservative substitution" is the replacement of an amino acid with another amino acid that has the same net electronic charge and approximately the same size and shape. Amino acids with aliphatic or substituted aliphatic amino acid side chains have approximately the same size when the total number carbon and heteroatoms in their side chains differs by no more than about four. They have approximately the same shape when the number of branches in the their side chains differs by no more than one. Amino acids with phenyl or substituted phenyl groups in their side chains are considered to have about the same size and shape. Listed below are five groups of amino acids. Replacing an amino acid in a polypeptide with another amino acid from the same group results in a conservative substitution:

[0023] Group I: glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, and non-naturally occurring amino acids with C1-C4 aliphatic or C1-C4 hydroxyl substituted aliphatic side chains (straight chained or monobranched).

[0024] Group II: glutamic acid, aspartic acid and non-naturally occurring amino acids with carboxylic acid substituted C1-C4 aliphatic side chains (unbranched or one branch point).

[0025] Group III: lysine, omithine, arginine and non-naturally occurring amino acids with amine or guanidino substituted C1-C4 aliphatic side chains (unbranched or one branch point).

[0026] Group IV: glutamine, asparagine and non-naturally occurring amino acids with amide substituted C1-C4 aliphatic side chains (unbranched or one branch point).

[0027] Group V: phenylalanine, phenylglycine, tyrosine and tryptophan.

[0028] A "highly conservative substitution" is the replacement of an amino acid with another amino acid that has the same functional group in the side chain and nearly the same size and shape. Amino acids with aliphatic or substituted aliphatic amino acid side chains have nearly the same size when the total number carbon and heteroatoms in their side chains differs by no more than two. They have nearly the same shape when they have the same number of branches in the their side chains. Example of highly conservative substitutions include valine for leucine, threonine for serine, aspartic acid for glutamic acid and phenylglycine for phenylalanine. Examples of substitutions which are not highly conservative include alanine for

valine, alanine for serine and aspartic acid for serine.

[0029] Other NPAR agonists include small organic molecules which bind and activate NPAR. Agonists of this type can be conveniently identified with high through-put screening, e.g., with assays that assess the ability of molecules to stimulate cell proliferation when added to fibroblasts in the presence of submitogenic concentrations of thrombin or molecules that activate protein kinase C or with assays that assess the ability of these molecules to compete with .sup.125I-thrombin to cells with surface NPAR receptors, as disclosed in Glenn et al., supra, U.S. Pat. Nos. 5,352,664 and 5,500,412. The entire teachings for Glenn et al., and U.S. Pat. Nos. 5,352,664 and 5,500,412 are incorporated herein by reference.

[0030] The term "NPAR agonist" also includes compounds and combinations of compounds known to activate NPAR. Examples are disclosed in U.S. Pat. Nos. 5,352,664 and 5,500,412 and include thrombin and DIP-alpha-thrombin.

[0031] NPAR agonists used in the method of the present invention are typically administered as one component in a pharmaceutical composition to the site in need of cartilage growth, repair or regeneration. Administering to the site in need of treatment means that the pharmaceutical composition containing the NPAR agonist is administered in sufficient proximity to the site in need of treatment so that cartilage growth or cartilage regeneration occurs at the site (e.g., a greater amount of cartilage growth or better quality of cartilage growth in the presence of the NPAR agonist than in its absence).

[0032] In one means of administration, the pharmaceutical composition is a solution comprising the NPAR agonist and a suitable carrier. The solution is applied directly to or in near proximity to the site in need of treatment. Administration of the solution can be conveniently accomplished, for example, intraarticularly by syringe, in close proximity to the damaged tissue by syringe or through a surgical opening. Standard pharmaceutical formulation techniques may be employed such as those described in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa. Suitable pharmaceutical carriers for include, for example, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like.

[0033] In another means of administration, the pharmaceutical composition comprises the NPAR agonist and an implantable biocompatible carrier. A biocompatible carrier should be non-toxic, non-inflammatory, non-immunogenic and devoid of other undesired reactions at the implantation site. Suitable carriers also provide for release of the active ingredient and preferably for a slow, sustained release over time at the implantation site.

[0034] A number of synthetic biodegradable polymers can serve as carriers with sustained release characteristics. Examples of these polymers include poly .alpha.-hydroxy esters such as polylactic acid/polyglycolic acid copolymers and polyanhydrides.

[0035] Polylactic acid/polyglycolic acid (PLGA) homo and copolymers are well known in the art as sustained release vehicles. The rate of release can be adjusted by the skilled artisan by variation of polylactic acid to polyglycolic acid ratio and the molecular weight of the polymer (see Anderson, et al., Adv. Drug Deliv. Rev. 28:5 (1997), the entire teachings of which are incorporated herein by reference). The incorporation of poly(ethylene glycol) into the polymer blend allows further attenuation of the release profile of the active ingredient (see Cleek et al., J. Control Release 48:259 (1997), the entire teachings of which are incorporated herein by reference). Suitable implantable PLGA polymers for use as carriers for cartilage growth factors are described in U.S. Pat. Nos. 6,013,853, 5,607,474 and 5,876,452, the entire teachings of which are incorporated herein by reference.

[0036] Polyanhydrides, shown in Structural Formula (II), have well defined degradation and release characteristics that can be controlled by including varying amounts of hydrophobic or hydrophilic monomers such as sebacic acid and 1,3-bis(p-carboxyphenoxy)propane (see Leong et al., J. Biomed. Mater. Res. 19:941 (1985), the entire teachings of which are incorporated herein by reference). To

improve mechanical strength, anhydrides are often copolymerized with imides to form polyanhydride-co-imides. Examples of polyanhydride-co-imides that are suitable for orthopaedic applications are poly(trimellitylimido-glycine-c-o-1,6-bis(carboxyphenoxy)hexane and pyromellityimidoalanine: 1,6-bis(p-carboxyphenoxy)hexane copolymers. 1

[0037] The pharmaceutical compositions can be shaped as desired in anticipation of surgery or shaped by the physician or technician during surgery. It is preferred to shape the matrix to span a tissue defect and to take the desired form of the new tissue. In the case of cartilage repair of large defects, it is desirable to use dimensions that span the defect. After implantation, the material is slowly absorbed by the body and is replaced by cartilage in the shape of or very nearly the shape of the implant.

[0038] In one aspect, the carrier is a porous matrix into which progenitor cells may migrate. Cells can often attach to such porous matrices, which can then serve as a scaffolding for tissue growth and thereby accelerate the rate of bone growth. Chondrocytes can be applied to such matrices prior to implant to further accelerate healing. Collagen or a collagen gel is an example of a suitable porous matrix.

[0039] In another aspect, the carrier is a viscous solution or gel that is injectable intraarticuarly or at the site in need of treatment. Hyaluronic acid is an example of a carrier of this type. Hyaluronic acid products are commercially available and include ORTHOVISC developed by Anika, SYNVISC, developed by Biomatrix, HYALGAN, developed by Fidia and ARTZ, developed by Seikagaku. Pluronic gel is another example of this type of carrier. Pluronic gels are nontxoic block copolymers of ethylene oxide and propylene oxide. They exhibit thermosetting properties that allow them to exist as viscous liquids at room temperatures, but as gels at body temperatures. Injectable compositions can be applied directly to the site in need of treatment without the need for invasive surgery. Polymers of poly(ethylene oxide) and copolymers of ethylene and propylene oxide are also suitable as injectable matrices (see Cao et al, J. Biomater. Sci 9:475 (1998) and Sims et al., Plast Reconstr.Surg. 98:843 (196), the entire teachings of which are incorporated herein by reference).

[0040] A "therapeutically effective amount" is the quantity of NPAR agonist (or chondrocytes) which results in greater cartilage growth or repair in the presence of the NPAR agonist than in its absence. Alternatively or addition, a "therapeutically effective amount" is the quantity of NPAR agonist (or chondrocytes) which results in alleviation of the pain and/or lack of function associated with the cartilage damage. Typically, the agonist (or chondrocytes) is administered for a sufficient period of time to achieve the desired therapeutic or effect. The amount administered will depend on the amount of cartilage growth that is desired, the health, size, weight, age and sex of the subject and the release characteristics of the pharmaceutical formulation. Typically, between about 0.1 .mu.g per day and about 1 mg per day of NPAR agonist (preferably between about 5 .mu.g per day and about 100 .mu.g per day) is administered by continuous release or by direct application to the site in need of carilage growth or repair.

[0041] A "subject" is preferably a human, but can also be an animal in need of treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, pigs, horses and the like) and laboratory animals (e.g., rats, mice, guinea pigs and the like).

[0042] NPAR agonists can be used to accelerate the growth or to maintain the functionality of isolated chondrocytes. In one embodiment, NPAR agonists can be added to tissue culture medium to stimulate proliferation and provide for more rapid proliferation and/or to prevent apoptotic death or senescence of cells often encountered when primary cell isolates are place in culture. In another embodiment, because the NPAR agonists appear to stimulate matrix production, such NPAR agonists could be used to maintain the differentiated functionality of chondrocytes in culture. NPAR agonists can be used alone in standard defined tissue culture medium or as a supplement to tissue culture medium containing serum or other growth factor to provide additive or synergistic effects on the in vitro production or maintenance of chondrocytes. A sufficient quantity of the NPAR agonist is added to the culture

to provide more rapid growth or to maintain greater functionality of the chondrocytes than in the absence of the agonist, i.e., a "stimulatory amount". Typically, between about 0.1 .mu.g/ml and about 100 .mu.g/ml of NPAR agonist is used.

[0043] Chondrocytes cultured in the presence of an NPAR agonists can also be used to treat cartilage damage by administering a therapeutically effective amount of the chondrocytes to the site in need of treatment. With respect to chondrocytes, "therapeutically effective" also means which results in greater cartilage growth or repair with the treatment than in its absence. The administration of chondrocytes to treat cartilage damage is described in U.S. Pat. No. 4,846,835, the entire teachings of which are incorporated herein by reference.

[0044] Thrombin peptide derivatives can be synthesized by solid phase peptide synthesis (e.g., BOC or FMOC) method, by solution phase synthesis, or by other suitable techniques including combinations of the foregoing methods. The BOC and FMOC methods, which are established and widely used, are described in Merrifield, J. Am. Chem. Soc. 88:2149 (1963); Meienhofer, Hormonal Proteins and Peptides, C. H. Li, Ed., Academic Press, 1983, pp. 48-267; and Barany and Merrifield, in The Peptides, E. Gross and J. Meienhofer, Eds., Academic Press, New York, 1980, pp. 3-285. Methods of solid phase peptide synthesis are described in Merrifield, R. B., Science, 232: 341 (1986); Carpino, L. A. and Han, G. Y., J. Org. Chem., 37: 3404 (1972); and Gauspohl, H. et al., Synthesis, 5: 315 (1992)). The teachings of these six articles are incorporated herein by reference in their entirety.

[0045] The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

[0046] Details of Experiments

[0047] Chondrocytes are the primary cell type found in cartilage. In cartilage these cells are normally quiescent, or non-proliferative, and have relatively low metabolic rates. Following injury to cartilage these cells do not readily participate in the repair process. Due to the avascular nature of cartilage, these cells presumably would not see thrombin as an initiator of the repair process. The following examples demonstrate that chondrocytes have thrombin receptors and that compounds that activate NPAR stimulate chondrocyte proliferation and synthesis of matrix proteoglycans.

EXAMPLE 1

Thrombin Binding to Rat Chondrocytes

[0048] Primary cultures of rat articular chondrocytes were isolated and prepared for in vitro analysis using established methods (see Kuettner, K E., et.al., J. Cell Biology 93: 743-750, 1982). Briefly, cartilage pieces were dissected from the shoulder of rats and the pieces were digested with trypsin for one hour and with collagenase for three hours in tissue culture medium (DMEM) at 37 C with stirring. The cells were plated in flasks at high density (50,000 cells/cm sq.) and were culture in DMEM containing antibiotics an ascorbic acid at 37.degree. C. in an atmosphere of 5% CO.sub.2.

[0049] The specific binding of .sup.125I thrombin to chondrocytes was carried out using established thrombin receptor binding assays as disclosed in U.S. Pat. No. 5,352,664 and Carney, D H and Cunningham, D D, Cell 15:1341-1349, 1978. Briefly, highly purified human thrombin was iodinated and added to cultures of chondrocytes with or without unlabeled thrombin to correct for nonspecific binding. By incubating cells with different concentrations of labeled thrombin and measuring the amount of thrombin bound to cells and the amount of free thrombin in the medium it is possible to estimate the number of receptors per cell and the affinity of thrombin for that binding site.

[0050] Scatchard analysis of the labeled thrombin binding from three separate

experiments suggest that rat chondrocytes express an average of 3000 very high affinity binding sites (100 pM affinity) and 230,000 high affinity sites (27 nM).

EXAMPLE 2A

NPAR Agonist Stimulation of Bovine Chondrocyte Proliferation

[0051] Primary cultures of bovine chondrocytes were prepared using the procedure described for rat chondrocytes in Example 1. The cultures were subcultured into 24 well plastic dishes at a low density and placed in 1% serum. Addition of the NPAR agonist TP508 to these cultures at concentrations of 1.0 or 10 .mu.g/ml by itself did not stimulate cell proliferation. In contrast, addition of these concentrations of TP508 together with a small amount of thrombin co-mitogen, resulted in a small, but significant ($p<0.05$) increase in cell number relative to that seen in thrombin alone after three days in culture.

EXAMPLE 2B

NPAR Agonist Stimulation of Bovine Chondrocyte Proteoglycan Synthesis

[0052] To determine the effect of NPAR agonists on proteoglycan synthesis, bovine chondrocytes were seeded into 96 well plates at a density of 2.times.10.sup.5 cells per well and cultured in DMEM with 10% fetal calf serum. After establishment of these multi-layer cultures, the medium was replaced daily with DMEM containing 1% serum with indicated concentrations of TP508 from 1 to 100 .mu.g per ml (Table 1). After 6 days in culture with daily changes of culture medium with or without TP508, .sup.35S sulfate was added to the medium and incubation continued for an additonal 24 hours. As shown in Table 1, treatment with high concentrations of TP508 (100 .mu.g per ml) increased .sup.35S sulfate incorporation relative to untreated cells by more than 10-fold.

1TABLE 1

Effect of the NPAR agonist TP508 on .sup.35S sulfate incorporation in bovine chondrocyte cultures.

Treatment	Mean CPM 1% Serum	Std. Dev of Mean
Control	4975	3552
TP508 (1 .mu.g/ml)	4701	2692
TP508 (10 .mu.g/ml)	6960	3265
TP508 (100 .mu.g/ml)	81946	13783

EXAMPLE 3A

NPAR Agonist Stimulation of Proliferation Synthesis in Cultured Rat Articular Chondrocytes

[0053] Rat articular chondrocytes were isolated from slices of rat articualar shoulder cartilage utilizing trypsin and collagenase digestions as described in Example 1. Preparations of chondrocyte "3-dimensional" alginate bead cultures were established using established techniques as described by Guo et. al., (Conn. Tiss. Res. 19:277-297, 1998). Following removal of cells from tissue culture flasks with trypsin, the cells were suspended in an alginate gel (1.2% w/v) and slowly expressed

through a 22 gauge needle in a dropwise fashion into 102 mM CaCl.sub.2. As the drops contact the CaCl.sub.2 there is a nearly instantaneous polymerization of the alginate to create a gel bead. The beads were then washed three times in DMEM culture medium and transferred to 35 mm dishes and maintained in culture at 37 C in a 5% CO.sub.2 atmosphere by feeding with culture medium every two days.

[0054] The effect of NPAR agonist TP508 on chondrocyte cell proliferation after three days in 3-dimensional alginate culture was determined by removing beads from 35 mm dishes, washing them with 0.9% saline, and dissolving the alginate beads by adding 1 ml of 55 mM sodium citrate, 0.15 M NaCl at 37.degree. C. for 10 minutes. Cell number was determined by diluting the 1 ml of dissolved beads 1:10 with phosphate buffered saline (PBS) and counting the cells with a Z-series Coulter Counter. As shown in Table 2, TP508 by itself stimulated proliferation of chondrocytes in 3 dimensional culture.

2TABLE 2

Effect of the NPAR agonist TP508 on Proliferation of Rat Chondrocytes in 3-D Bead Culture.

Treatment	Cells/bead After 3 days	Std. dev	% Increase over Control
Control	6238	688	
TP508 30 nM	7463	167	19.7
TP508 300 nM	8882	148	42.4
TP508 3 .mu.M	8866	4	42.1
TP508 30 .mu.M	7772	258	24.6

EXAMPLE 3B

NPAR Agonist Stimulation of Proteoglycan Synthesis in Cultured Rat Articular Chondrocytes

[0055] To determine the effectos of the NPAR agonist TP508 on proteoglycan synthesis, 3-dimensional alginate cultures were prepared as described above and assayed for incorporation of [.sup.35S]-sulfate. Bead cultures were exposed to indicated concentrations of TP508 as well as [.sup.35S]-sulfate (20 .mu.Ci/ml) and with daily medium changes and were harvested on days 7 for [.sup.35S]-sulfate incorporation. At each time point 5-10 beads were removed, washed 3.times. with 0.9% saline, dissolved by adding 0.5 ml of 55 mM sodium citrate, 0.15 M NaCl at 37 C for 10 minutes as described above, and counted in a liquid scintillation counter. [.sup.35S]-sulfate incorporation was normalized in each sample for number of beads added. As shown in Table 3, TP508 treatment alone at a concentration of 300 nM (about 0.7 .mu.g per ml), stimulated [.sup.35S]-sulfate incorporation about 50% over controls. There was also a large stimulation by 30 .mu.M TP508 (about 70 .mu.g per ml), however, there was a large relative standard deviation in measurements at this concentration.

3TABLE 3

Effect of the NPAR agonist TP508 on [.sup.35S]-sulfate incorporation into proteoglycans.

Std. % Increase
Treatment CPM/bead dev over Control

Control 665 24
TP508 30 nM 829 87 24.7
TP508 300 nM
1008 29 51.6
TP508 3 .mu.M 827 9 24.1
TP508 30 .mu.M 1153
519 73.3

EXAMPLE 4

Preparation of Polylactic Acid/Polyglycolic Acid Copolymer Microspheres of TP508

[0056] A double emulsion technique was used to prepare microspheres of polylactic acid/polyglycolic acid copolymer (PLGA) containing TP508. Briefly, the matrix components were dissolved in methylene chloride and TP508 was dissolved in water. The two were gradually mixed together while vortexing to form a water-in-oil (W/O) emulsion. Polyvinyl alcohol (0.3% in water) was added to the emulsion with further vortexing to form the second emulsion (O/W), thereby forming a double emulsion: an O/W emulsion comprised of PLGA droplets, and within those droplets, a second disperse phase consisting of TP508 in water. Upon phase separation, the PLGA droplets formed discrete microspheres containing cavities holding TP508. To cause phase separation of the microspheres, a 2% isopropyl alcohol solution was added. The particles were collected by centrifugation, and then lyophilized to remove residual moisture. The composition of the matrix was varied to form microspheres with different release kinetics (Table 4).

4TABLE 4

Composition of different microsphere formulations
Polymer % % polyethylene
Formulation PLA:PGA
M. Wt. TP508 glycol

A 50:50 46,700 5 0
B 50:50
7,200 5 0
C 50:50 46,700 5 5
D 50:50 46,700 5 0
E
75:25 120,000 5 0

[0057] The mean diameter of the microspheres was measured in a Coulter counter and the drug entrapment efficiency was measured by spectrophotometric assay at 276 nm following dissolution of a weighed sample of microspheres in methylene chloride and extraction of the released drug into water (Table 5).

5TABLE 5

Formulation diameter and drug entrapment efficiency

Formulation	Diameter, .mu.m	TP508 Entrapment, %
A	26.0	53.8
B	16.2	27.1
C	17.6	58.9
D	23.9	42.6
E	25.8	36.2

[0058] To measure TP508 release from the different PLGA matrices, 20 mg of microspheres were placed in 1.0 ml of PBS contained in 1.5 ml polypropylene microcentrifuge tubes. Tubes were incubated at 37.degree. C. and shaken at 60 rpm. At various times, the tubes were centrifuged and the supernatant containing released TP508 was removed and frozen for subsequent analysis. Fresh PBS was added to the microspheres and incubation was continued. TP508 in the supernatant was measured by absorbance at 276 nm. For each formulation, quadruplicate release determinations were performed. Formulations B and D showed no detectable drug release during 28 days of incubation at 37.degree. C. The remaining formulations all released detectable amounts of TP508, although in all cases the amount of drug released fell below detectable limits (<1 .mu.g/mg matrix/day) within 3-4 days. Formulations A and C showed the greatest release of TP508, releasing 60-80% of the entrapped drug over 3-4 days. Formulation C showed the fastest release kinetics and was chosen for testing in the rabbit cartilage defect model described in Example 5.

EXAMPLE 5

The NPAR Agonist TP508 Stimulates Cartilage Growth in Rabbit Models

[0059] Young, male New Zealand rabbits (2-3 kilograms) (n=15) were anesthetized and given bilateral, medial longitudinal parapatellar arthrotomies. The skin, subcutaneous tissue and joint capsule were incised, using electrocautery to minimize bleeding. The joint surface was exposed by lateral dislocation of the patella. A 3-mm diameter, 1-2-mm deep full-thickness defect was made in the trochlear groove of the femur using a surgical drill and pointed stainless steel drill bit. The aim was to extend the defect into the subchondral plate without piercing the subchondral bone.

[0060] The rabbits were divided into three groups. For each rabbit, both right and left trochlear groove defects were filled with the same treatment. For this study, TP508 was formulated into PLGA controlled release microspheres, prepared as described in Example 4 (Formulation C). The microspheres were mixed with sufficient Pluronic F68 gel (5% w/v) to bind the spheres together into a paste-like consistency that could easily be packed into the defect. The control group received PLGA microspheres without TP508 in both defects. The treated groups received microspheres containing either 10 or 50 mg of TP508/defect. One rabbit from each group was sacrificed at 4 weeks, 2 from each group were sacrificed at 6 weeks and the remaining animals were sacrificed at 9 weeks. Samples were fixed and processed for histological analysis.

[0061] At the time of sacrifice, there appeared to be considerable fibrous granulation tissue and no evidence of white cartilage-like material in the control defects. In contrast, the defect had a nearly uniform, dense, white material filling in the defects from the 10 .mu.g treated group and 50 .mu.g group. By 6 weeks post-surgery, the macroscopic differences between treated and control defects were not so pronounced.

[0062] Histology of the four week samples showed that indeed the control defects were filled with what appeared to represent early granulation tissue including inflammatory and fibroblastic cells. In contrast, the 10 and 50 microgram treated defects appeared to have a large number of chondrocytes and early signs of cartilage formation. This effect was seen more dramatically at week six. Controls had a small amount of connective tissue, yet little evidence of cartilage repair. In contrast, in both the 10 .mu.g and 50 .mu.g treated defects, there appeared to be good integration with hyaline cartilage forming at the top of the defect and extensive subchondral bone repair.

[0063] Nine-week TP508 treated defects exhibited a predominantly hyaline matrix with evidence of significant aggrecan content as shown by positive safranin-O staining. In most instances there was no difference in aggrecan content between the repair site and native tissue. Histological results were quantitatively assessed using a grading system adapted by Freed, et al., J. Biomed. Materials Res. 28:891-899 (1944) from the scheme of O'Driscoll, et al., J. Bone Joint Surg. 126:1448-1452 (2000) with a maximum score of 25 for normal articular cartilage. Experimental TP508 treated defects scored mean averages that were significantly higher than control defects (Table 6).

6TABLE 6

Histology Scoring For Articular Defect Study

Milligrams of TP508	Repair Score .+-. SE
0	9.4 .+-. 1.6
10	18.6 .+-. 1.4
50	19.8 .+-. 1.0

[0064] Peptide treated defects repaired with smooth articular surfaces and were typically well bonded at the junction between repair and native tissue. The quality of control repair tissue was characterized as mostly fibrocartilage with poor quality joint surfaces. Integration at the junction between repair and native tissue was usually poor. Overall, the quality of cartilage repaired with TP508 was significantly enhanced over control non-treated defects. This improved quality of repair tissue should lead to more durable and functional restoration of joint biomechanics and reduction in the incidence of osteoarthritis in patients suffering from traumatic cartilage injuries.

[0065] While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS:

What is claimed is:

1. A method of stimulating cartilage growth or repair at a site in a subject in need of such growth or repair, said method comprising the step of administering to the site a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor.

2. The method of claim 1 wherein the site is an arthritic joint.

3. The method of claim 1 wherein the site is being treated for cartilage damage or

loss.

4. The method of claim 1 wherein the site is being treated for cartilage damage or loss due to traumatic injury.

5. The method of claim 1 wherein the agonist is a thrombin peptide derivative comprising a polypeptide represented by the following structural formula or a physiologically functional equivalent thereof: Asp-Ala-R; wherein R is a serine esterase conserved sequence.

6. The method of claim 5 wherein the thrombin peptide derivative has between about 12 and about 23 amino acids.

7. The method of claim 6 wherein the serine esterase conserved sequence has the amino acid sequence of SEQ ID NO. 1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-- Pro-Phe-Val), or a C-terminal truncated fragment thereof having at least six amino acids, provided that zero, one, two or three amino acids in the serine esterase conserved sequence differ from the corresponding position of SEQ ID NO 1.

8. The method of claim 6 wherein the serine esterase conserved sequence has the amino acid sequence of SEQ ID NO. 1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-- Pro-Phe-Val), or a C-terminal truncated fragment thereof having at least nine amino acids, provided that zero, one or two of the amino acids in the serine esterase conserved region are conservative susbstitutions of the corresponding amino acid in SEQ ID NO 1.

9. The method of claim 6 wherein the serine esterase conserved sequence has the amino acid sequence of SEQ ID NO 2 (Cys-X.sub.1-Gly-Asp-Ser-Gly-G-
ly-Pro-X.sub.2-Val, wherein X.sub.1 is Glu or Gln and X.sub.2 is Phe, Met, Leu, His or Val), or a C-terminus truncated fragment of SEQ ID NO 2, said fragment having at least six amino acids.

10. The method of claim 9 wherein the thrombin peptide derivative comprises the amino acid sequence Arg-Gly-Asp-Ala (SEQ ID NO 3).

11. The method of claim 10 wherein the thrombin peptide derivative comprises the amino acid sequence Arg-Gly-Asp-Ala-Cys-X.sub.1-Gly-Asp-Ser-
-Gly-Gly-Pro-X.sub.2-Val (SEQ ID NO 4), wherein X.sub.1 is Glu or Gln and X.sub.2 is Phe, Met, Leu, His or Val.

12. The method of claim 11 wherein the thrombin peptide derivative has the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-C-
ys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val- (SEQ ID NO 5), or an N-terminal truncated fragment thereof, provided that zero, one, two or three amino acids at positions 1-9 in the thrombin peptide derivative differ from the amino acid at the corresponding position of SEQ ID NO 5.

13. The method of claim 11 wherein the thrombin peptide derivative has the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-C-
ys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val- (SEQ ID NO 5), or an N-terminal truncated fragment thereof, provided that zero, one or two amino acids at positions 1-9 in the thrombin peptide derivative are conservative substitutions of the amino acid at the corresponding position of SEQ ID NO 5.

14. The method of claim 6, wherein the subject is administered a therapeutically effective amount of a physiologically equivalent thrombin derivative peptide comprising a C-terminal amide.

15. The method of claim 6, wherein the subject is administered a physiologically functional equivalent thrombin derivative peptide comprising
Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gl-
y-Asp-Ser-Gly-Gly-Pro-Phe-Val-CONH.sub.2 (SEQ ID NO: 6).

16. The method of claim 6, wherein the subject is administered a physiologically functional equivalent thrombin derivative peptide consisting of
Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-

-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-CONH.sub.2 (SEQ ID NO: 6).

17. The method of claim 12 wherein the thrombin peptide derivative is administered in a pharmaceutical composition additionally comprising an implantable, biocompatible carrier.

18. The method of claim 17 wherein the carrier comprises a polylactic acid/polyglycolic acid homopolymer or copolymer.

19. A method of stimulating cartilage growth or repair at a site in a subject in need there such growth or repair, said method comprising the step of administering to the site a therapeutically effective amount of a peptide having the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-A-
sp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO 5).

20. A method of stimulating cartilage growth at an arthritic joint in a subject, said method comprising the step of administering to the site a therapeutically effective amount of a peptide having the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-G-
ly-Gly-Pro-Phe-Val (SEQ ID NO 5).

21. A method of stimulating cartilage growth in a subject at a site being treated for cartilage loss, said method comprising the step of administering to the site a therapeutically effective amount of a peptide having the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-C-
ys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO 5).

22. A method of stimulating cartilage growth in a subject at a site being treated for cartilage loss due to traumatic injury, said method comprising the step of administering to the site a therapeutically effective amount of a peptide having the sequence Ala-Gly-Try-Lys-Pro-Asp-
-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO 5).

23. A method for culturing chondrocytes in vitro, the improvement comprising culturing the chondrocytes in the presence of a stimulating amount of an NPAR agonist.

24. The method of claim 23, further comprising the step of administering a therapeutically effective amount of the cultured chondrocytes to a site in a subject in need of cartilage repair or growth.

25. A method of stimulating cartilage growth or repair at a site in a subject in need of such growth or repair, said method comprising the step of administering to the site a peptide having the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-G-
ly-Gly-Pro-Phe-Val-CONH.sub.2 (SEQ ID NO: 6).

26. A method of stimulating cartilage growth at an arthritic joint in a subject, said method comprising the step of administering to the site a therapeutically effective amount of a peptide having the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-G-
ly-Gly-Pro-Phe-Val-CONH.sub.2 (SEQ ID NO: 6).

27. A method of stimulating cartilage growth in a subject at a site being treated for cartilage loss, said method comprising the step of administering to the site a therapeutically effective amount of a peptide having the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-C-
ys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-CONH.sub.2 (SEQ ID NO: 6).

28. A method of stimulating cartilage growth in a subject at a site being treated for cartilage loss due to traumatic injury, said method comprising the step of administering to the site a therapeutically effective amount of a peptide having the sequence Ala-Gly-Try-Lys-Pro-Asp-
-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-CONH.- sub.2 (SEQ ID NO: 6).

No. 60/217,583, filed Jul. 12, 2000, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0003] Human alpha-thrombin appears to have growth-promoting activity for a wide variety of cells from various tissues. For example, alpha-thrombin has been shown to initiate proliferation of fibroblastic cells in culture without addition of serum or other purified growth factors, to synergize with epidermal growth factor in certain hamster fibroblasts and human endothelial cells, to initiate cell division or DNA synthesis in mammalian lens epithelial and spleen cells and actuate monocytes and neutrophils. Yet, the use of thrombin as a growth factor and its potential importance to wound healing has not been widely acclaimed. In part, this may be due to the complexity of thrombin's involvement with coagulation, platelet activation, and initiation of cell proliferation as well as to the complex regulation of thrombin and thrombin-like molecules by serum protease inhibitors and by cell-released protease nexins. This complexity and high degree of physiologic regulation, however, supports the potential importance of this initiation pathway in wound healing.

[0004] Thrombin may also play a role in both normal revascularization and migration of cells from the blood to the site of injury and the abnormal metastasis and angiogenesis associated with tumors. The ability of thrombin to increase endothelial cell proliferation and alter the barrier function of blood vessels may contribute to angiogenesis and inflammation at sites of tissue injury.

[0005] Thrombin derivative peptides have been described by the present inventors for the agonizing and antagonizing thrombin and/or thrombin receptor activity, such as in the treatment of wounds. U.S. Pat. No. 5,500,412 or 5,352,664, the contents of which are incorporated herein by reference in their entirety. However, the patent does not teach the novel use of the thrombin derivative peptides for the treatment of damaged cardiac tissue, for revascularization, or for inhibition of vascular occlusion and restenosis.

SUMMARY OF THE INVENTION

[0006] The invention relates to methods for promoting cardiac tissue or myocardium repair, promoting vascularization or inhibiting vascular occlusion or restenosis. The method comprises administering to the cardiac tissue or blood vessels a therapeutically effective amount of an angiogenic thrombin derivative peptide. In a preferred embodiment, the peptide is a peptide described in U.S. Pat. No. 5,500,412 or 5,352,664, the contents of which are incorporated herein by reference in their entirety. For example, the peptide can preferably comprises a thrombin receptor binding domain having the sequence Arg-Gly-Asp-Ala (SEQ ID NO. 2); and a serine esterase conserved sequence. Preferred serine esterase conserved sequences comprise Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-- Val (SEQ ID NO. 2). In yet a more preferred embodiment, the thrombin derivative peptide comprises the amino acid sequence: Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO. 3), such as a peptide which consists of the amino acid sequence Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO. 3). The peptide having the sequence of SEQ ID NO. 3 is also referred to herein as "TP508").

[0007] Alternatively, the thrombin derivative peptide is a physiologically functional equivalent of the thrombin derivative peptide comprising the amino acid sequence of SEQ ID NO: 3. In a particular embodiment, the thrombin derivative peptide comprises the modified amino acid sequence: Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-CONH.sub.2 (SEQ ID NO: 4). In a particular embodiment, the thrombin derivative peptide consists of the modified amino acid sequence: Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly--Asp-Ser-Gly-Gly-Pro-Phe-Val-CONH.sub.2 (SEQ ID NO: 4).

[0008] The peptide can preferably be administered during or following cardiac surgery, for example by direct or catheter-mediated injection into damaged or

ischemic cardiac tissue as a soluble peptide or in a sustained release formulation.

[0009] The invention also relates to a method of stimulating revascularization or vascular endothelial cell proliferation comprising administering to cardiac tissue a therapeutically effective amount of an angiogenic thrombin derivative peptide, as described herein.

[0010] The invention also relates to a method of preventing vascular occlusion or restenosis comprising administering a therapeutically effective amount of the angiogenic thrombin receptor binding peptide to blood vessels, for example, by systemic injection, by delivering the peptides to sites of vascular injury by catheter, or by attachment of the peptide to stents.

BRIEF DESCRIPTION OF THE FIGURES

[0011] FIG. 1 is a graph showing that increasing concentrations of TP508 (peptide having the amino acid sequence of SEQ ID NO. 3) stimulates the proliferation of human microvascular endothelial cells in vitro. The graph shows the cell count 48 hours after being administered various concentrations of TP508 (indicated in .mu.g/ml).

[0012] FIG. 2 is a graph showing that increasing concentrations of TP508 stimulates the migration of microvascular endothelial cells on plastic. The graph shows the distance migrated by the cells after being administered various concentrations of TP508 (indicated in .mu.g/ml).

[0013] FIG. 3 is a graph showing changes in cardiac function in TP508 treated and control pigs in porcine model of cardiac ischemia.

DETAILED DESCRIPTION OF THE INVENTION

[0014] Cardiovascular diseases are generally characterized by an impaired supply of blood to the heart or other target organs. Myocardial infarction (MI) result from narrowed or blocked coronary arteries in the heart which starves the heart of needed nutrients and oxygen. When the supply of blood to the heart is compromised, cells respond by generating compounds that induce the growth of new blood vessels so as to increase the supply of blood to the heart. These new blood vessels are called collateral blood vessels. The process by which new blood vessels are induced to grow out of the existing vasculature is termed angiogenesis, and the substances that are produced by cells to induce angiogenesis are the angiogenic factors.

[0015] When heart muscle is deprived of oxygen and nutrients due to vascular occlusion, the heart muscle tissue becomes ischemic and looses its ability to contract and function. This loss of function may be restored by natural signals from the ischemic heart muscle that induce angiogenic revascularization through development of collateral vessels that bypass the occlusion. This revascularization or angiogenesis involves the stimulation of endothelial cell proliferation and migration and budding off of new blood vessels. In many cases, however, the natural signals are not sufficient to cause collateral vessel growth and the ischemic tissue can become fibrotic or necrotic. If this process is not reversed by procedures to open the occluded vessels or further induction of collateral blood vessels, the heart may become totally disfunctional and require transplantation.

[0016] The peptides described herein can be employed to induce angiogenic proliferation and migration of endothelial cells resulting in formation of new capillaries and collateral vessels to help restore function to damaged or ischemic heart tissue. These peptides may preferably be directly injected into or applied to heart tissue during open chest procedures for bypass surgery or insertion of ventricular assist devices or delivered by catheter injection into the heart as a soluble peptide or in a sustained release formulation.

[0017] Endothelial cell proliferation, such as that which occurs in angiogenesis, is also useful in preventing or inhibiting restenosis following balloon angioplasty. The balloon angioplasty procedure often injures the endothelial cells lining the inner walls of blood vessels and disrupts the integrity of the vessel wall. Smooth

muscle cells and inflammatory cells often infiltrate into the injured blood vessels causing a secondary obstruction in a process known as restenosis. Stimulation of the proliferation and migration of the endothelial cells located at the periphery of the balloon-induced damaged area in order to cover the luminal surface of the vessel with a new monolayer of endothelial cells would potentially restore the original structure of the blood vessel.

[0018] Preferably, endothelialization comprises re-endothelialization after angioplasty, to reduce, inhibit or prevent restenosis. Those of skill in the art will recognize that patients treated according to the methods of the present invention may be treated with or without a stent.

[0019] An inflatable balloon catheter with peptide coating the balloon or a catheter that directly injects the peptide into the wall of the vessel may also be employed to deliver the substance to a targeted artery.

[0020] Balloon angioplasty is a common treatment of ischemic heart disease which involves the inflation of a balloon in a clogged blood vessel in order to open the blocked blood vessel. Unfortunately, this method of treatment results in injury to the endothelial cells lining the inner walls of blood vessels often leading to restenosis. The peptides described herein can be employed to induce proliferation and migration of the endothelial cells located at the periphery of the balloon induced damaged area in order to cover the luminal surface of the vessel with a new monolayer of endothelial cells, hoping to restore the original structure of the blood vessel. Coronary angioplasty is frequently accompanied by deployment of an intravascular stent to help maintain vessel function and avoid restenosis. Stents have been coated with heparin to prevent thrombosis until the new channel formed by the stent can endothelialize. The peptides described herein can be applied directly to the stent, using methods known to those of skill in the art. The peptides can be locally applied or systemically administered to enhance endothelialization of the vessel or vessel wall and/or to modulate other processes to inhibit or reduce thrombosis and restenosis.

[0021] The present invention preferably employs synthetic or naturally derived polypeptide agonists of thrombin receptor mediated events. Both of these classes of agents possess a thrombin receptor binding domain which includes a segment of the polypeptide that is capable of selectively binding to the high-affinity thrombin receptor. This segment of the polypeptide includes a sequence of amino acids homologous to a tripeptide cell binding domain of fibronectin.

[0022] In addition to the thrombin receptor binding domain, the stimulatory (agonistic) polypeptides possess a sequence of amino acids having sequences derived from the N-terminal amino acids of a dodecapeptide previously shown to be highly conserved among serine proteases. However, the inhibitory polypeptides do not include these serine esterase-conserved sequences.

[0023] For example, the invention provides a number of polypeptides useful in promoting cardiac tissue repair. For such applications, the invention provides a polypeptide derivative of thrombin (or a functional equivalent of such a derivative) which has a thrombin receptor binding domain as well as a domain with a serine esterase conserved sequence of at least 12 amino acids. The invention also provides a polypeptide compound of at least 23 L-amino acids which has both a thrombin receptor binding domain and a domain with a serine esterase conserved amino acid sequence.

[0024] In one embodiment, the invention provides for several polypeptides containing specific amino acid sequences, such as a polypeptide compound in which the thrombin receptor binding domain includes the L-amino acid sequence Arg-Gly-Asp-Ala (SEQ ID NO. 1) together with the serine esterase conserved amino acid sequence, Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Ph- e-Val (SEQ ID NO. 2). In a preferred embodiment, the polypeptide compound includes the L-amino acid sequence Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Ar-
g-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO. 3). The polypeptide compound can be modified by amidation of the carboxy terminus. For example, SEQ ID NO: 3 can be amidated as follows:

Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-G-ly-Gly-Pro-Phe-Val-CONH.sub.2 (SEQ ID NO: 4).

[0025] The invention also provides for a pharmaceutical composition for promoting tissue repair which includes a therapeutically effective concentration of any of the compounds described above combined with a pharmaceutically acceptable excipient. Typically, such compositions include, for example, sufficient concentrations of the polypeptides to effect a stimulatory action on the thrombin receptor as demonstrated herein. Thus, such compositions should typically include sufficient concentrations to obtain levels of the polypeptides at the target site which are shown in vitro to stimulate the receptor. When endogenous levels of a secondary signal are believed to be inadequate, compositions may be employed which further include the addition of a therapeutically effective concentration of VEGF, alpha-thrombin, gamma-thrombin or other growth factors. Such combinations may exert an additive or synergistic effect. In certain cases, if tissue damage is so extensive that cells capable of responding to the polypeptides are not present in sufficient quantities, it is expected that responsive cells could be co-injected to provide a therapeutically effective combination.

[0026] Suitable carriers also provide for release of the active ingredient and preferably for a slow, sustained release over time at the target site. A number of synthetic biodegradable polymers can serve as carriers with sustained release characteristics. Examples of these polymers include poly .alpha.-hydroxy esters such as polylactic acid/polyglycolic acid homopolymers and copolymers, polyphosphazenes (PPHOS), polyanhydrides and poly(propylene fumarates).

[0027] Polylactic acid/polyglycolic acid (PLGA) homo and copolymers are well known in the art as sustained release vehicles. The rate of release can be adjusted by the skilled artisan by variation of polylactic acid to polyglycolic acid ratio and the molecular weight of the polymer (see Anderson, et al., Adv. Drug Deliv. Rev. 28:5 (1997), the entire teachings of which are incorporated herein by reference). The incorporation of poly(ethylene glycol) into the polymer as a blend to form microparticle carriers allows further attenuation of the release profile of the active ingredient (see Cleek et al., J. Control Release 48:259 (1997), the entire teachings of which are incorporated herein by reference). PGLA microparticles are often mixed with pluronic gels or collagen to prevent aggregation and to make the microparticles suitable for direct injection.

[0028] PPHOS polymers contain alternating nitrogen and phosphorous with no carbon in the polymer backbone, as shown below in Structural Formula (I): 1

[0029] The properties of the polymer can be adjusted by suitable variation of side groups R and R' that are bonded to the polymer backbone. For example, the degradation of and drug release by PPHOS can be controlled by varying the amount of hydrolytically unstable side groups. With greater incorporation of either imidazolyl or ethylglycinato substituted PPHOS, for example, an increase in degradation rate is observed (see Laurencin et al., J Biomed Mater. Res. 27:963 (1993), the entire teachings of which are incorporated herein by reference), thereby increasing the rate of drug release.

[0030] Polyanhydrides, shown in Structural Formula (II), have well defined degradation and release characteristics that can be controlled by including varying amounts of hydrophobic or hydrophilic monomers such as sebacic acid and 1,3-bis(p-carboxyphenoxy)propane (see Leong et al., J. Biomed. Mater. Res. 19:941 (1985), the entire teachings of which are incorporated herein by reference). 2

[0031] Poly(propylene fumarates) (PPF) are highly desirable biocompatible implantable carriers because they are an injectable, in situ polymerizable, biodegradable material. "Injectable" means that the material can be injected by syringe through a standard needle used for injecting pastes and gels. PPF, combined with a vinyl monomer (N-vinyl pyrrolidinone) and an initiator (benzoyl peroxide), forms an injectable solution that can be polymerized in situ (see Suggs et al., Macromolecules 30:4318 (1997), Peter et al., J. Biomater. Sci. Poly,. Ed. 10:363 (1999) and Yaszemski et al., Tissue Eng. 1:41 (1995), the entire teachings of which are incorporated herein by reference).

Chemical Indexing M1 *01*
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H8 J0 J011 J1 J111 J171 J371 K0 L2 L250
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Chemical Indexing M1 *04*
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NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
NEWS 16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 20	EVENTLINE will be removed from STN
NEWS 28	Mar 24	PATDPAFULL now available on STN
NEWS 29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 30	Apr 11	Display formats in DGENE enhanced
NEWS 31	Apr 14	MEDLINE Reload
NEWS 32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 33	Apr 21	Indexing from 1947 to 1956 being added to records in CA/CAPLUS
NEWS 34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 35	Apr 28	RDISCLOSURE now available on STN
NEWS 36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 39	May 16	CHEMREACT will be removed from STN
NEWS 40	May 19	Simultaneous left and right truncation added to WSCA
NEWS 41	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation

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 NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

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FILE 'HOME' ENTERED AT 16:33:26 ON 23 MAY 2003

=> file uspatful, dgene, embase, medline, biosis
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

FILE 'USPATFULL' ENTERED AT 16:33:59 ON 23 MAY 2003
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FILE 'BIOSIS' ENTERED AT 16:33:59 ON 23 MAY 2003
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=> s non-proteolytically activated thrombin receptor
L1          15 NON-PROTEOLYTICALLY ACTIVATED THROMBIN RECEPTOR

=> d l1 ti abs ibib tot

L1   ANSWER 1 OF 15  USPATFULL
TI     Stimulation of cartilage growth with agonists of the non-
       proteolytically activated thrombin
       receptor
AB     Disclosed is a method of stimulating cartilage growth, repair or
       regeneration at a site in a subject in need of such growth, repair or
       regeneration. The method comprises the step of administering a
       therapeutically effective amount of an agonist of the non-
       proteolytically activated thrombin
       receptor to the site.

       Also disclosed is a method of stimulating the proliferation and
       expansion of chrondrocytes in vitro. The method comprises culturing
       chrondrocytes in the presence of a stimulating amount of an NPAR
       agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER:       2002:344424  USPATFULL
```

TITLE: Stimulation of cartilage growth with agonists of the **non-proteolytically activated thrombin receptor**

INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES

PATENT ASSIGNEE(S): Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002198154	A1	20021226
APPLICATION INFO.:	US 2002-50688	A1	20020116 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-909348, filed on 19 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
LINE COUNT: 862
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 2 OF 15 USPATFULL
TI Stimulation of bone growth with thrombin peptide derivatives
AB Disclosed is a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method comprises the step of administering a therapeutically effective amount of an agonist of the **non-proteolytically activated thrombin receptor** to the site.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:322044 USPATFULL
TITLE: Stimulation of bone growth with thrombin peptide derivatives

INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Simmons, David J., St. Louis, MO, UNITED STATES
Yang, Jinping, Galveston, TX, UNITED STATES
Redin, William R., Dickinson, TX, UNITED STATES

PATENT ASSIGNEE(S): Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002182205	A1	20021205
APPLICATION INFO.:	US 2002-50692	A1	20020116 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-909122, filed on 19 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219300P	20000719 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS: 46

EXEMPLARY CLAIM: 1
LINE COUNT: 846
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 3 OF 15 USPATFULL
TI Stimulation of bone growth with thrombin peptide derivatives
AB Disclosed is a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method comprises the step of administering a therapeutically effective amount of an agonist of the **non-proteolytically activated thrombin receptor** to the site.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:236005 USPATFULL
TITLE: Stimulation of bone growth with thrombin peptide derivatives
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Simmons, David J., St. Louis, MO, UNITED STATES
Yang, Jinping, Galveston, TX, UNITED STATES
Redin, William R., Dickinson, TX, UNITED STATES
PATENT ASSIGNEE(S): The Board of Regents, The University of TX. System (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002128202	A1	20020912
APPLICATION INFO.:	US 2001-909122	A1	20010719 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219300P	20000719 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1
LINE COUNT: 797
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 4 OF 15 USPATFULL
TI Stimulation of cartilage growth with agonists of the **non-proteolytically activated thrombin receptor**
AB Disclosed is a method of stimulating cartilage growth, repair or regeneration at a site in a subject in need of such growth, repair or regeneration. The method comprises the step of administering a therapeutically effective amount of an agonist of the **non-proteolytically activated thrombin receptor** to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an NPAR agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:78716 USPATFULL
TITLE: Stimulation of cartilage growth with agonists of the **non-proteolytically activated thrombin receptor**
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES

	Stiernberg, Janet, Paris, TX, UNITED STATES Bergmann, John, Galveston, TX, UNITED STATES			
PATENT ASSIGNEE(S):	The Board of Regents, The University of Texas System (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002042373	A1	20020411	
APPLICATION INFO.:	US 2001-909348	A1	20010719	(9)
	NUMBER		DATE	
PRIORITY INFORMATION:	US 2000-219800P		20000720	(60)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799			
NUMBER OF CLAIMS:	21			
EXEMPLARY CLAIM:	1			
LINE COUNT:	836			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 5 OF 15 DGENE (C) 2003 THOMSON DERWENT

TI Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor -

AN AAU78376 Peptide DGENE

AB The invention describes a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method involves administering an agonist to stimulate bone growth at a site in a subject (e.g. a farm animal, companion animal or laboratory animal), in need of osteoinduction, such as the site in need of a bone graft in a subject, a segmental bone gap, a bone void or a non-union fracture. This sequence represents a thrombin peptide derivative obtained from a serine esterase that can stimulate or activate the **non-proteolytically activated thrombin receptor**.

ACCESSION NUMBER:	AAU78376 Peptide DGENE
TITLE:	Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor -
INVENTOR:	Carney D H; Crowther R S; Simmons D J; Yang J; Redin W R
PATENT ASSIGNEE:	(TEXA)UNIV TEXAS SYSTEM.
PATENT INFO:	WO 2002005836 A2 20020124 27p
APPLICATION INFO:	WO 2001-US22641 20010718
PRIORITY INFO:	US 2000-219300P 20000719
DOCUMENT TYPE:	Patent
LANGUAGE:	English
OTHER SOURCE:	2002-303796 [34]
DESCRIPTION:	Thrombin peptide derivative TP508.

L1 ANSWER 6 OF 15 DGENE (C) 2003 THOMSON DERWENT

TI Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor -

AN AAU78375 Peptide DGENE

AB The invention describes a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method involves administering an agonist to stimulate bone growth at a site in a subject (e.g. a farm animal, companion animal or laboratory animal), in need of osteoinduction, such as the site in need of a bone graft in a subject, a segmental bone gap, a bone void or a non-union fracture. This sequence represents a thrombin peptide derivative obtained from a serine esterase that can stimulate or activate the **non-proteolytically**

activated thrombin receptor.

ACCESSION NUMBER: AAU78375 Peptide DGENE
TITLE: Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor -
INVENTOR: Carney D H; Crowther R S; Simmons D J; Yang J; Redin W R
PATENT ASSIGNEE: (TEXA) UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002005836 A2 20020124 27p
APPLICATION INFO: WO 2001-US22641 20010718
PRIORITY INFO: US 2000-219300P 20000719
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-303796 [34]
DESCRIPTION: Thrombin peptide derivative #2.

L1 ANSWER 7 OF 15 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor -
AN AAU78374 Peptide DGENE
AB The invention describes a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method involves administering an agonist to stimulate bone growth at a site in a subject (e.g. a farm animal, companion animal or laboratory animal), in need of osteoinduction, such as the site in need of a bone graft in a subject, a segmental bone gap, a bone void or a non-union fracture. This sequence represents a thrombin peptide derivative obtained from a serine esterase that can stimulate or activate the **non-proteolytically activated thrombin receptor.**

ACCESSION NUMBER: AAU78374 Peptide DGENE
TITLE: Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor -
INVENTOR: Carney D H; Crowther R S; Simmons D J; Yang J; Redin W R
PATENT ASSIGNEE: (TEXA) UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002005836 A2 20020124 27p
APPLICATION INFO: WO 2001-US22641 20010718
PRIORITY INFO: US 2000-219300P 20000719
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-303796 [34]
DESCRIPTION: Thrombin peptide derivative #1.

L1 ANSWER 8 OF 15 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor -
AN AAU78373 Peptide DGENE
AB The invention describes a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method involves administering an agonist to stimulate bone growth at a site in a subject (e.g. a farm animal, companion animal or laboratory animal), in need of osteoinduction, such as the site in need of a bone graft in a subject, a segmental bone gap, a bone void or a non-union fracture. This sequence represents a serine esterase conserved sequence obtained from a serine esterase that can stimulate or activate the **non-proteolytically activated thrombin receptor.**

ACCESSION NUMBER: AAU78373 Peptide DGENE
TITLE: Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering

agonist of activated thrombin receptor -
INVENTOR: Carney D H; Crowther R S; Simmons D J; Yang J; Redin W R
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002005836 A2 20020124 27p
APPLICATION INFO: WO 2001-US22641 20010718
PRIORITY INFO: US 2000-219300P 20000719
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-303796 [34]
DESCRIPTION: Serine esterase conserved sequence #2.

L1 ANSWER 9 OF 15 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor -
AN AAU78372 Peptide DGENE
AB The invention describes a method of stimulating bone growth at a site in a subject in need of osteoinduction. The method involves administering an agonist to stimulate bone growth at a site in a subject (e.g. a farm animal, companion animal or laboratory animal), in need of osteoinduction, such as the site in need of a bone graft in a subject, a segmental bone gap, a bone void or a non-union fracture. This sequence represents a serine esterase conserved sequence obtained from a serine esterase that can stimulate or activate the **non-proteolytically activated thrombin receptor**.
ACCESSION NUMBER: AAU78372 Peptide DGENE
TITLE: Stimulating bone growth at a site in a subject in need of osteoinduction, such as a site of bone graft, segmental bone gap, bone void or non-union structure, by administering agonist of activated thrombin receptor -
INVENTOR: Carney D H; Crowther R S; Simmons D J; Yang J; Redin W R
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002005836 A2 20020124 27p
APPLICATION INFO: WO 2001-US22641 20010718
PRIORITY INFO: US 2000-219300P 20000719
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-303796 [34]
DESCRIPTION: Serine esterase conserved sequence #1.

L1 ANSWER 10 OF 15 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of **non-proteolytically activated thrombin receptor** -
AN AAE20159 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an agonist of **non-proteolytically activated thrombin receptor** (NPAR). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of NPAR agonist to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is human thrombin peptide derivative which serves as a NPAR agonist.
ACCESSION NUMBER: AAE20159 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of **non-proteolytically activated thrombin receptor** -
INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.

PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Human thrombin peptide derivative #2.

L1 ANSWER 11 OF 15 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of **non-proteolytically activated thrombin receptor** -
AN AAE20158 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an agonist of **non-proteolytically activated thrombin receptor** (NPAR). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of NPAR agonist to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is human thrombin peptide derivative which serves as a NPAR agonist.
ACCESSION NUMBER: AAE20158 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of **non-proteolytically activated thrombin receptor** -
INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Human thrombin peptide derivative #1.

L1 ANSWER 12 OF 15 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of **non-proteolytically activated thrombin receptor** -
AN AAE20157 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an agonist of **non-proteolytically activated thrombin receptor** (NPAR). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of NPAR agonist to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is human thrombin peptide. The derivatives of thrombin peptide which serves as a NPAR agonist.
ACCESSION NUMBER: AAE20157 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of **non-proteolytically activated thrombin receptor** -
INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719

PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Human thrombin peptide.

L1 ANSWER 13 OF 15 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of **non-proteolytically activated thrombin receptor** -
AN AAE20156 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an agonist of **non-proteolytically activated thrombin receptor** (NPAR). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of NPAR agonist to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is serine esterase conserved peptide. This sequence is present in the thrombin peptide derivatives which serve as a NPAR agonist.
ACCESSION NUMBER: AAE20156 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of **non-proteolytically activated thrombin receptor** -
INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Serine esterase conserved peptide #2.

L1 ANSWER 14 OF 15 DGENE (C) 2003 THOMSON DERWENT
TI Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of **non-proteolytically activated thrombin receptor** -
AN AAE20155 peptide DGENE
AB The invention relates to a method of stimulating growth and repair of cartilage. The method involves administering to the site, an agonist of **non-proteolytically activated thrombin receptor** (NPAR). The method is used in human or veterinary medicine for the treatment of arthritic joints and damage/loss of cartilage caused by traumatic injury. Also chondrocytes may be cultured in presence of NPAR agonist to provide cells for implantation at sites requiring growth/repair of cartilage. The present sequence is serine esterase conserved peptide. This sequence is present in the thrombin peptide derivatives which serve as a NPAR agonist.
ACCESSION NUMBER: AAE20155 peptide DGENE
TITLE: Stimulating growth and repair of cartilage, useful for treating e.g. arthritis, by local administration of an agonist of **non-proteolytically activated thrombin receptor** -
INVENTOR: Carney D H; Crowther R S; Stiernberg J; Bergmann J
PATENT ASSIGNEE: (TEXA)UNIV TEXAS SYSTEM.
PATENT INFO: WO 2002007748 A2 20020131 28p
APPLICATION INFO: WO 2001-US22668 20010719
PRIORITY INFO: US 2000-219800P 20000720
DOCUMENT TYPE: Patent

LANGUAGE: English
OTHER SOURCE: 2002-268953 [31]
DESCRIPTION: Serine esterase conserved peptide #1.

L1 ANSWER 15 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Purification and characterization of the high affinity non-proteolytically activated (NPAR) thrombin receptor.
ACCESSION NUMBER: 2003:156453 BIOSIS
DOCUMENT NUMBER: PREV200300156453
TITLE: Purification and characterization of the high affinity non-proteolytically activated (NPAR) thrombin receptor.
AUTHOR(S): Bergmann, J. S. (1); Laird, A. C.; Tsulaia, T. V.; Keherly, M. J.; Carney, D. H.
CORPORATE SOURCE: (1) Human Biological Chemistry and Genetics, Medical Branch, University Texas, Galveston, TX, USA USA
SOURCE: Molecular Biology of the Cell, (Nov. 2002, 2002) Vol. 13, No. Supplement, pp. 290a. print.
Meeting Info.: 42nd Annual Meeting of the American Society for Cell Biology San Francisco, CA, USA December 14-18, 2002 American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

=> e carney, d/au
E1 1 CARNEY Y L/AU
E2 1 CARNEY YVONNE L/AU
E3 0 --> CARNEY, D/AU
E4 1 CARNEYALE G J/AU
E5 1 CARNEZ B/AU
E6 1 CARNEZ BERNARD/AU
E7 4 CARNFELDT THURE/AU
E8 1 CARNFILL HUPP K/AU
E9 4 CARNI A/AU
E10 1 CARNI ANDRAU/AU
E11 10 CARNI ANDRAZ/AU
E12 2 CARNI CATSADIMA I/AU

=> e crowther, R/au
E1 1 CROWTHER WILLIAM H/AU
E2 4 CROWTHER WILLIAM R/AU
E3 0 --> CROWTHER, R/AU
E4 1 CROWTHERS I/AU
E5 2 CROWTHERS K C/AU
E6 1 CROWTHERS KEVIN C/AU
E7 2 CROWTHERS V/AU
E8 1 CROWTHERT C A/AU
E9 1 CROWTHERT R L/AU
E10 1 CROWWELL G L/AU
E11 1 CROXALL DEREK F/AU
E12 1 CROXALL DEREK FRANCIS/AU

=> e stiernberg, j/au
E1 4 STIERNBERG JANET/AU
E2 1 STIERNBERG JANET S/AU
E3 0 --> STIERNBERG, J/AU
E4 10 STIERNBORG M/AU
E5 58 STIERNER U/AU
E6 4 STIERNER ULRIKA/AU
E7 4 STIERNET F/AU
E8 3 STIERNET N/AU
E9 1 STIERNHDM B J/AU
E10 1 STIERNHDM B J N/AU

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E11          1     STIERNHDM B J NICLAS/AU
E12          3     STIERNHOLM B J/AU

=> s e1
L2           4 "STIERNBERG JANET"/AU

=> s e2
L3           1 "STIERNBERG JANET S"/AU

=> d l2 ti abs ibib tot

L2   ANSWER 1 OF 4  USPATFULL
TI     Stimulation of cartilage growth with agonists of the non-proteolytically
       activated thrombin receptor
AB     Disclosed is a method of stimulating cartilage growth, repair or
       regeneration at a site in a subject in need of such growth, repair or
       regeneration. The method comprises the step of administering a
       therapeutically effective amount of an agonist of the
       non-proteolytically activated thrombin receptor to the site.

       Also disclosed is a method of stimulating the proliferation and
       expansion of chrondrocytes in vitro. The method comprises culturing
       chrondrocytes in the presence of a stimulating amount of an NPAR
       agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER:       2002:344424  USPATFULL
TITLE:                  Stimulation of cartilage growth with agonists of the
                        non-proteolytically activated thrombin receptor
INVENTOR(S):            Carney, Darrell H., Dickinson, TX, UNITED STATES
                        Crowther, Roger S., League City, TX, UNITED STATES
                          Stiernberg, Janet, Paris, TX, UNITED STATES
                        Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S):     Univ. of Texas System, Board of Regents, Austin, TX,
                        UNITED STATES, 78701 (U.S. corporation)

                             NUMBER        KIND    DATE
                        ---------------- ------ --------
PATENT INFORMATION:     US 2002198154      A1   20021226
APPLICATION INFO.:      US 2002-50688      A1   20020116  (10)
RELATED APPLN. INFO.:   Continuation of Ser. No. US 2001-909348, filed on 19
                        Jul 2001, PENDING

                               NUMBER        DATE
                        ------------------ --------
PRIORITY INFORMATION:   US 2000-219800P    20000720 (60)
DOCUMENT TYPE:          Utility
FILE SEGMENT:           APPLICATION
LEGAL REPRESENTATIVE:   HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA
                        ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS:       28
EXEMPLARY CLAIM:        1
LINE COUNT:             862
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2   ANSWER 2 OF 4  USPATFULL
TI     Stimulation of cartilage growth with agonists of the non-proteolytically
       activated thrombin receptor
AB     Disclosed is a method of stimulating cartilage growth, repair or
       regeneration at a site in a subject in need of such growth, repair or
       regeneration. The method comprises the step of administering a
       therapeutically effective amount of an agonist of the
       non-proteolytically activated thrombin receptor to the site.
```

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an NPAR agonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:78716 USPATFULL
TITLE: Stimulation of cartilage growth with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S): The Board of Regents, The University of Texas System (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002042373	A1	20020411
APPLICATION INFO.:	US 2001-909348	A1	20010719 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 836
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 3 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Acceleration of full-thickness wound healing in normal rats by the synthetic thrombin peptide, TP508.
AB Thrombin is an essential factor in hemostasis, inflammation, and tissue repair. The synthetic thrombin peptide, TP508, binds to high-affinity thrombin receptors and mimics cellular effects of thrombin at sites of tissue injury. Treatment of full-thickness excisional wounds in normal rats with a single topical application of 0.1 mug TP508 (14 pmol/cm2) reproducibly accelerates wound closure, yielding wounds that on average close 39% more than controls by day 7 ($p < 0.001$). Wounds treated with 1.0 mug TP508 are 35% and 43% ($p < 0.001$) smaller than controls on day 7 and 10, respectively. The early rate of closure is apprx40% greater in TP508-treated than vehicle-treated wounds (20 versus 14 mm2/day) and remains higher through day 7. Breaking strength after closure is slightly greater (15-23%) in wounds treated with TP508 than with saline alone. Histologic comparisons show that TP508 enhances recruitment of inflammatory cells to the wound site within 24 hours post-injury. TP508 treatment also augments revascularization of injured tissue, as evidenced at day 7 by the larger size of functional vessels in the granulation tissue and by the directed development of blood vessels to wounds. These studies raise the possibility that TP508 may be clinically useful in management of open wounds.
ACCESSION NUMBER: 2000:336305 BIOSIS
DOCUMENT NUMBER: PREV200000336305
TITLE: Acceleration of full-thickness wound healing in normal rats by the synthetic thrombin peptide, TP508.
AUTHOR(S): **Stiernberg, Janet**; Norfleet, Andrea M.; Redin, William R.; Warner, W. Scott; Fritz, Richard R.; Carney, Darrell H. (1)
CORPORATE SOURCE: (1) Department of Human Biological Chemistry and Genetics, University of Texas Medical Branch, 301 University Blvd.,

E1	1		BERGMANN Y/AU
E2	1		BERGMANN YU/AU
E3	0	-->	BERGMANN, J/AU
E4	2		BERGMANNN L/AU
E5	1		BERGMANNOV A B/AU
E6	16		BERGMANNOVA E/AU
E7	1		BERGMANNOVA EVA/AU
E8	17		BERGMANNOVA V/AU
E9	1		BERGMANNS H/AU
E10	1		BERGMANNT G/AU
E11	2		BERGMANOVA EVA/AU
E12	2		BERGMANOVA V/AU

Galveston, TX, 77555-0645 USA
SOURCE: Wound Repair and Regeneration, (May June, 2000) Vol. 8, No. 3, pp. 204-215. print.
ISSN: 1067-1927.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

L2 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI The role of thrombin and thrombin receptor activating peptide (TRAP-508) in initiation of tissue repair.
ACCESSION NUMBER: 1993:487012 BIOSIS
DOCUMENT NUMBER: PREV199345098237
TITLE: The role of thrombin and thrombin receptor activating peptide (TRAP-508) in initiation of tissue repair.
AUTHOR(S): **Stiernberg, Janet**; Redin, William R.; Warner, W. Scott; Carney, Darrell H. (1)
CORPORATE SOURCE: (1) Dep. Hum. Biological Chem. and Genetics, Univ. Texas Med. Branch, Galveston, TX 77555-0645 USA
SOURCE: Thrombosis and Haemostasis, (1993) Vol. 70, No. 1, pp. 158-162.
ISSN: 0340-6245.
DOCUMENT TYPE: General Review
LANGUAGE: English

=> d l3 ti abs ibib tot

L3 ANSWER 1 OF 1 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Accelerated recruitment of inflammatory cells to dermal wounds by the thrombin peptide TP508.
ACCESSION NUMBER: 2000:63096 BIOSIS
DOCUMENT NUMBER: PREV200000063096
TITLE: Accelerated recruitment of inflammatory cells to dermal wounds by the thrombin peptide TP508.
AUTHOR(S): Norfleet, Andrea M. (1); Redin, William R. (1); Sower, Laurie E. (1); **Stiernberg, Janet S. (1)**; Carney, Darrell H. (1)
CORPORATE SOURCE: (1) University of Texas Medical Branch, 301 University Blvd, Galveston, TX USA
SOURCE: Molecular Biology of the Cell, (Nov., 1999) Vol. 10, No. SUPPL., pp. 317a.
Meeting Info.: 39th Annual Meeting of the American Society for Cell Biology Washington, D.C., USA December 11-15, 1999 The American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 16:33:26 ON 23 MAY 2003)

FILE 'USPATFULL, DGENE, EMBASE, MEDLINE, BIOSIS' ENTERED AT 16:33:59 ON 23 MAY 2003
L1 15 S NON-PROTEOLYTICALLY ACTIVATED THROMBIN RECEPTOR
E CARNEY, D/AU
E CROWTHER, R/AU
E STIERNBERG, J/AU
L2 4 S E1
L3 1 S E2

=> e bergmann, j/au

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
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NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
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NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
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NEWS 13	Nov 18	DKILIT has been renamed APOLLIT
NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
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NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 20	EVENTLINE will be removed from STN
NEWS 28	Mar 24	PATDPAFULL now available on STN
NEWS 29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 30	Apr 11	Display formats in DGENE enhanced
NEWS 31	Apr 14	MEDLINE Reload
NEWS 32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 33	Apr 21	Indexing from 1947 to 1956 being added to records in CA/CAPLUS
NEWS 34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 35	Apr 28	RDISCLOSURE now available on STN
NEWS 36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 39	May 16	CHEMREACT will be removed from STN
NEWS 40	May 19	Simultaneous left and right truncation added to WSCA
NEWS 41	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation

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 NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
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=> file medline, uspatful, dgene, embase, scisearch, wpids, hcaplus, fsta, jicst,
japio, ceaba, cen, biosis
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.42       0.42

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FILE 'CEN' ENTERED AT 16:10:58 ON 23 MAY 2003
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FILE 'BIOSIS' ENTERED AT 16:10:58 ON 23 MAY 2003

=> s cartilage growth
L1 2291 CARTILAGE GROWTH

=> s l1 and repair
L2 495 L1 AND REPAIR

=> s l2 and stimulation
L3 214 L2 AND STIMULATION

=> s l3 and agonist
L4 70 L3 AND AGONIST

=> s l4 and thrombin peptide
L5 3 L4 AND THROMBIN PEPTIDE

=> d l5 ti abs ibib tot

L5 ANSWER 1 OF 3 USPATFULL
TI **Stimulation** of **cartilage growth** with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating **cartilage growth**, **repair** or regeneration at a site in a subject in need of such growth, **repair** or regeneration. The method comprises the step of administering a therapeutically effective amount of an **agonist** of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an NPAR **agonist**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:344424 USPATFULL
TITLE:	**Stimulation** of **cartilage growth** with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S):	Carney, Darrell H., Dickinson, TX, UNITED STATES Crowther, Roger S., League City, TX, UNITED STATES Stiernberg, Janet, Paris, TX, UNITED STATES Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S):	Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002198154	A1	20021226
APPLICATION INFO.:	US 2002-50688	A1	20020116 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-909348, filed on 19 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS:	28
EXEMPLARY CLAIM:	1

LINE COUNT: 862
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 2 OF 3 USPATFULL
TI **Stimulation** of **cartilage growth** with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating **cartilage growth**, **repair** or regeneration at a site in a subject in need of such growth, **repair** or regeneration. The method comprises the step of administering a therapeutically effective amount of an **agonist** of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an NPAR **agonist**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:78716 USPATFULL
TITLE: **Stimulation** of **cartilage growth** with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S): The Board of Regents, The University of Texas System (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002042373	A1	20020411	
APPLICATION INFO.:	US 2001-909348	A1	20010719	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-219800P	20000720	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 836
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2003 ACS
TI **Stimulation** of **cartilage growth** with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating **cartilage growth**, **repair** or regeneration at a site in a subject in need of such growth, **repair** or regeneration. The method comprises the step of administering a therapeutically effective amt. of an **agonist** of the non-proteolytically activated thrombin receptor (NPAR) to the site. Also disclosed is a method of stimulating the proliferation and expansion of chondrocytes in vitro. The method comprises culturing chondrocytes in the presence of a stimulating amt. of an NPAR **agonist**. The NPAR **agonist** TP508 (a **thrombin peptide** deriv.) stimulated **cartilage growth** in rabbits.
ACCESSION NUMBER: 2002:89846 HCAPLUS
DOCUMENT NUMBER: 136:145245
TITLE: **Stimulation** of **cartilage growth** with agonists of the

non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H.; Crowther, Roger S.; Stiernberg, Janet; Bergmann, John
PATENT ASSIGNEE(S): The Board of Regents, the University of Texas System, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002007748	A2	20020131	WO 2001-US22668	20010719
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002042373	A1	20020411	US 2001-909348	20010719
EP 1259598	A2	20021127	EP 2001-952846	20010719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002198154	A1	20021226	US 2002-50688	20020116

PRIORITY APPLN. INFO.:
US 2000-219800P P 20000720
US 2001-909348 A1 20010719
WO 2001-US22668 W 20010719

OTHER SOURCE(S): MARPAT 136:145245

=> d his

(FILE 'HOME' ENTERED AT 16:09:44 ON 23 MAY 2003)

FILE 'MEDLINE, USPATFULL, DGENE, EMBASE, SCISEARCH, WPIDS, HCAPLUS, FSTA, JICST-EPLUS, JAPIO, CEABA-VTB, CEN, BIOSIS' ENTERED AT 16:10:58 ON 23 MAY 2003

L1 2291 S CARTILAGE GROWTH
L2 495 S L1 AND REPAIR
L3 214 S L2 AND STIMULATION
L4 70 S L3 AND AGONIST
L5 3 S L4 AND THROMBIN PEPTIDE

=> s l4 and esterase
L6 4 L4 AND ESTERASE

=> d l6 ti abs ibib tot

L6 ANSWER 1 OF 4 USPATFULL
TI Novel genes encoding proteins having prognostic, diagnostic, preventive, therapeutic, and other uses
AB The invention provides isolated nucleic acid molecules and polypeptide molecules. The invention also provides antisense nucleic acid molecules, expression vectors containing the nucleic acid molecules of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid molecule of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and antibodies. Diagnostic, screening

and therapeutic methods utilizing compositions of the invention are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:38351 USPATFULL

TITLE: Novel genes encoding proteins having prognostic, diagnostic, preventive, therapeutic, and other uses

INVENTOR(S): Holtzman, Douglas A., Jamaica Plain, MA, UNITED STATES
Barnes, Thomas M., Brookline, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003027998	A1	20030206
APPLICATION INFO.:	US 2001-796753	A1	20010301 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-183175, filed on 30 Oct 1998, ABANDONED Continuation-in-part of Ser. No. US 2000-599596, filed on 22 Jun 2000, ABANDONED Division of Ser. No. US 1998-223546, filed on 30 Dec 1998, ABANDONED Division of Ser. No. US 1999-471179, filed on 23 Dec 1999, PENDING Continuation-in-part of Ser. No. US 1998-223546, filed on 30 Dec 1998, ABANDONED Continuation-in-part of Ser. No. US 1999-474072, filed on 29 Dec 1999, PENDING Continuation-in-part of Ser. No. US 1998-224246, filed on 30 Dec 1998, ABANDONED Continuation-in-part of Ser. No. US 1999-474071, filed on 29 Dec 1999, ABANDONED Continuation-in-part of Ser. No. US 1998-223094, filed on 30 Dec 1998, ABANDONED Continuation-in-part of Ser. No. US 2000-514010, filed on 25 Feb 2000, ABANDONED Continuation-in-part of Ser. No. US 1999-259388, filed on 26 Feb 1999, ABANDONED Continuation-in-part of Ser. No. US 2000-516745, filed on 1 Mar 2000, ABANDONED Continuation-in-part of Ser. No. US 2000-597993, filed on 19 Jun 2000, PENDING Continuation-in-part of Ser. No. US 1999-336536, filed on 18 Jun 1999, PENDING Continuation-in-part of Ser. No. US 2000-630334, filed on 31 Jul 2000, PENDING Continuation-in-part of Ser. No. US 1999-365164, filed on 30 Jul 1999, ABANDONED Continuation-in-part of Ser. No. US 2000-665666, filed on 20 Sep 2000, PENDING Continuation-in-part of Ser. No. US 1999-399723, filed on 20 Sep 1999, ABANDONED Continuation-in-part of Ser. No. US 2000-667751, filed on 21 Sep 2000, PENDING Continuation-in-part of Ser. No. US 1999-409634, filed on 30 Sep 1999, ABANDONED Continuation-in-part of Ser. No. US 2000-572002, filed on 15 May 2000, PENDING Continuation-in-part of Ser. No. US 1999-312359, filed on 14 May 1999, ABANDONED Continuation-in-part of Ser. No. US 2000-606565, filed on 29 Jun 2000, PENDING Continuation-in-part of Ser. No. US 1999-342687, filed on 29 Jun 1999, ABANDONED Continuation-in-part of Ser. No. US 2000-606317, filed on 29 Jun 2000, PENDING Continuation-in-part of Ser. No. US 1999-345464, filed on 30 Jun 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-122458P	19990301 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: PENNIE AND EDMONDS, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 100362711

NUMBER OF CLAIMS: 27

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 536 Drawing Page(s)

LINE COUNT: 22222
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 2 OF 4 USPATFULL
TI **Stimulation** of **cartilage growth** with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating **cartilage growth**, **repair** or regeneration at a site in a subject in need of such growth, **repair** or regeneration. The method comprises the step of administering a therapeutically effective amount of an **agonist** of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an NPAR **agonist**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:344424 USPATFULL
TITLE: **Stimulation** of **cartilage growth** with agonists of the non-proteolytically activated thrombin receptor
INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
Crowther, Roger S., League City, TX, UNITED STATES
Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES
PATENT ASSIGNEE(S): Univ. of Texas System, Board of Regents, Austin, TX, UNITED STATES, 78701 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002198154	A1	20021226
APPLICATION INFO.:	US 2002-50688	A1	20020116 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-909348, filed on 19 Jul 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX 9133, CONCORD, MA, 01742-9133
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
LINE COUNT: 862
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 3 OF 4 USPATFULL
TI **Stimulation** of **cartilage growth** with agonists of the non-proteolytically activated thrombin receptor
AB Disclosed is a method of stimulating **cartilage growth**, **repair** or regeneration at a site in a subject in need of such growth, **repair** or regeneration. The method comprises the step of administering a therapeutically effective amount of an **agonist** of the non-proteolytically activated thrombin receptor to the site.

Also disclosed is a method of stimulating the proliferation and expansion of chrondrocytes in vitro. The method comprises culturing chrondrocytes in the presence of a stimulating amount of an NPAR **agonist**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:78716 USPATFULL

TITLE: **Stimulation** of **cartilage** **growth** with agonists of the non-proteolytically activated thrombin receptor

INVENTOR(S): Carney, Darrell H., Dickinson, TX, UNITED STATES
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Stiernberg, Janet, Paris, TX, UNITED STATES
Bergmann, John, Galveston, TX, UNITED STATES

PATENT ASSIGNEE(S): The Board of Regents, The University of Texas System (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002042373	A1	20020411
APPLICATION INFO.:	US 2001-909348	A1	20010719 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-219800P	20000720 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: Carolyn S. Elmore, HAMILTON, BROOK, SMITH & REYNOLDS, P.C., Two Militia Drive, Lexington, MA, 02421-4799

NUMBER OF CLAIMS: 21

EXEMPLARY CLAIM: 1

LINE COUNT: 836

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2003 ACS

TI **Stimulation** of **cartilage** **growth** with agonists of the non-proteolytically activated thrombin receptor

AB Disclosed is a method of stimulating **cartilage** **growth**, **repair** or regeneration at a site in a subject in need of such growth, **repair** or regeneration. The method comprises the step of administering a therapeutically effective amt. of an **agonist** of the non-proteolytically activated thrombin receptor (NPAR) to the site. Also disclosed is a method of stimulating the proliferation and expansion of chondrocytes in vitro. The method comprises culturing chondrocytes in the presence of a stimulating amt. of an NPAR **agonist**. The NPAR **agonist** TP508 (a thrombin peptide deriv.) stimulated **cartilage** **growth** in rabbits.

ACCESSION NUMBER: 2002:89846 HCAPLUS

DOCUMENT NUMBER: 136:145245

TITLE: **Stimulation** of **cartilage** **growth** with agonists of the non-proteolytically activated thrombin receptor

INVENTOR(S): Carney, Darrell H.; Crowther, Roger S.; Stiernberg, Janet; Bergmann, John

PATENT ASSIGNEE(S): The Board of Regents, the University of Texas System, USA

SOURCE: PCT Int. Appl., 28 pp.
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PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002007748	A2	20020131	WO 2001-US22668	20010719

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002042373	A1	20020411	US 2001-909348		20010719
EP 1259598	A2	20021127	EP 2001-952846		20010719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
US 2002198154	A1	20021226	US 2002-50688		20020116
PRIORITY APPLN. INFO.:			US 2000-219800P	P	20000720
			US 2001-909348	A1	20010719
			WO 2001-US22668	W	20010719

OTHER SOURCE(S): MARPAT 136:145245